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Predictive Factors for Brachiocephalic and Brachiobasilic Arteriovenous Fistula Success – Role of Colour Doppler Ultrasound

António Pedro da Silva Pinto Gomes

Mentor: Evangelista Rocha, MD, PhD

Co-Mentor: Maria José Ferreira, MD

Original dissertation specifically prepared for attainment of the Master Degree in Epidemiology

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À minha família - a razão nobre que justifica só por si a minha existência.

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ABSTRACT

INTRODUCTION: End stage renal disease (ESRD) is increasing worldwide. Hemodialysis is the most frequent renal replacement therapy. Dysfunction and vascular access complications account for 20-30% of hospital admissions with high morbidity, high mortality and high economic burden. International societies recommend pre-operative colour Doppler ultrasound (CDUS) vascular mapping in addition to physical examination. It is not consensual whether pre-operative vascular mapping is associated with higher success in vascular access surgery. Current scientific evidence, based on clinical, anatomical and hemodynamic criteria, is insufficient to determine the best vascular access for each patient.

AIM: To evaluate pre-operative anatomical and hemodynamic parameters measured by Doppler ultrasound as predictors of brachiocephalic an brachiobasilic arteriovenous fistula early success.

METHODS: Observational, analytical, prospective analysis of patients (n=132) who underwent brachiocephalic or brachiobasilic AVF surgery between January 2016 and May 2017. Outcomes: primary patency at 48 hours, fistula success at six weeks and twelve weeks measured clinically and by CDUS. Variables: patient's demographics, comorbidities, medication, CDUS derived pre-operative parameters and immediate pre-operative hemodynamic parameters. Non-parametric statistic was used. Univariate analysis and multivariate analysis with logistic regression models were performed. ROC curve analyses were performed for independent predictive factors.

RESULTS: Primary patency at 48h was 91.7%, AVF success at 6 weeks was 71.3% and AVF success at 12 weeks was66.3%. There were no associations in

univariate and multivariate logistic regression analysis between AVF patency and AVF success and demographics, CKD factors and comorbidities.

Immediate pre-operative systolic blood pressure was an independent predictor of 48h patency with an optimized cut-off of 154mmHg (AUC=0.73; p=0.013; Youden index=0.40). Vein diameter with tourniquet was an independent predictor of AVF success at 6 weeks and 12 weeks with an optimized cut-off of 3.9mm (AUC=0.69; p=0.004; Youden index=0.29 and AUC=0.74; p<0.001; Youden index=0.38, respectively).

Paired analysis comparing 6 weeks and 12 weeks CDUS-derived parameters showed no statistical differences between AVF blood flow, peak systolic velocity and resistance index. Vein diameter was higher at 12 weeks' follow-up compared to 6 weeks (median=8.40mm (IQR=3.00) vs 7.40 (IQR=2.70), respectively; p<0.001).

CONCLUSIONS: AVF success was independent of demographics, CKD stage and comorbidities. Immediate pre-operative systolic blood pressure was an independent predictive factor for primary patency at 48h with an optimized cut-off of 154mmHg. Vein diameter with tourniquet was an independent predictive factor for fistula success at 6 and 12 weeks with an optimized cut-off of 3.9mm.

Key-words: Arteriovenous Fistula; Colour *Doppler* Ultrasound; Hemodialysis; Predictive factors; Primary Patency

PORTUGUESE ABSTRACT – RESUMO EM PORTUGUÊS

INTRODUÇÃO:

A prevalência da doença renal crónica (DRC) terminal tem aumentado mundialmente e estima-se que este aumento se intensifique na próxima década. De acordo com a Associação Renal Europeia – Associação Europeia de Diálise e Transplantação (ERA-EDTA) em 2014, cerca de 500000 doentes estavam sob terapêutica de substituição renal (TSR) e cerca de 70000 iniciaram uma TSR nesse ano.

Em Portugal, em 2016, 11738 doentes estavam sob hemodiálise (HD) como TSR. A HD representava em 2016, 60% das TSR utilizadas, correspondendo a um aumento de 40% na taxa de incidência nas últimas duas décadas.

Em 2016, em Portugal apenas 45,6% dos doentes que iniciaram hemodiálise tinham um acesso vascular definitivo funcional na primeira sessão.

A falência e as complicações cirúrgicas dos acessos vasculares são responsáveis por 20 a 30% dos internamentos e episódios de urgência entre os doentes hemodialisados. Para além das implicações na morbilidade e na qualidade de vida dos doentes, associam-se elevados custos económicos e sociais.

A otimização de modelos preditivos de sucesso da construção das fístulas arteriovenosas (FAV), combinando as variáveis demográficas e clínicas de um doente, com as características anatómicas e hemodinâmicas do leito vascular do braço, representam uma mais-valia na redução da morbilidade e custos associados à falência e complicações cirúrgicas.

O mapeamento vascular pré-operatório dos acessos vasculares definitivos para hemodiálise tem sido progressivamente estabelecido como *standard-of-care* e é

atualmente recomendado pelas sociedades científicas internacionais. No entanto, a qualidade da evidência disponível está longe da desejada.

O próximo passo na sustentabilidade da ecografia com Doppler no mapeamento vascular pré-operatório sistemático será a criação de recomendações para decisão cirúrgica com base nos valores do diâmetro arterial e venoso, débito arterial e pressão arterial em função das características clínicas de um dado doente.

OBJETIVO

O objetivo do estudo foi avaliar as características anatómicas e hemodinâmicas da artéria umeral e veia como fatores preditores de sucesso na construção de fistulas arteriovenosas proximais como primeiro acesso definitivo para hemodiálise.

MÉTODOS

Estudo observacional, prospetivo.

Foram incluídos os doentes adultos com DRC terminal referenciados para construção de fístula úmero-cefálica ou úmero-basílica como acesso vascular definitivo para hemodiálise após consentimento informado. Foram excluídos os doentes: sem informação em relação a ecografia com *Doppler*; com variantes anatómicas; com cirurgias prévias no membro ipsilateral; com complicações pós-operatórias com necessidade de revisão cirúrgica.

Foram definidos como *outcomes*: 1) a permeabilidade do acesso vascular às 48h, às 6 semanas e às 12 semanas; 2) o sucesso da fístula, medido por

ecografia com Doppler às 6 semanas e às 12 semanas definido como um diâmetro venoso ≥6 mm e um débito ≥600 ml/min.

Considerando 30% de falência/insucesso, de acordo com *Peduzzi et. al.*, são necessários um número mínimo de 134 doentes para que o estudo seja conclusivo.

Foram medidas as variáveis de caracterização demográfica; caracterização da doença renal crónica; relacionadas com as comorbilidades associadas; caracterização anatómica e hemodinâmica medidas por ecografia com *Doppler* pré-operatório (diâmetro de veia com garrote e sem garrote, diâmetro da artéria umeral, débito da artéria umeral); e caracterização do procedimento cirúrgico, nomeadamente, a pressão arterial imediatamente pré-operatória.

Análise Estatística: Descritiva e univariada paramétrica ou não-paramétrica após testar aproximação da distribuição das variáveis à distribuição Normal. Regressão logística considerando como variável dependente a permeabilidade às 48h, às 6 semanas e às 12 semanas e o sucesso da fístula às 6 semanas e às 12 semanas. Foram incluídas 4 variáveis dependentes por modelo de regressão em função da dimensão da amostra. Foram selecionadas para variáveis independentes aquelas com significância estatística na análise univariada ou com base na plausibilidade biológica de efeito. Foram analisadas as curvas ROC (*Receiver Operating Characteristic*) para as variáveis com significância estatística com definição de *cut-off* e índice de Youden.

Considerações Éticas: este estudo decorreu de acordo com os pressupostos da Declaração de Helsínquia. O protocolo de estudo e o consentimento informado foram aprovados pela Comissão de Ética da Faculdade de Medicina

de Lisboa e do Hospital Prof. Doutor Fernando da Fonseca. Todos os participantes deram o seu consentimento informado por escrito.

RESULTADOS

Entre Janeiro de 2016 e Junho de 2017 foram incluídos 160 doentes, dos quais 132 foram considerados elegíveis para o estudo. 69,2% do sexo masculino, idade mediana de 71 anos com um intervalo interquartil de 13 anos.

Após verificação dos pressupostos da estatística paramétrica verificou-se que nem todas as variáveis apresentavam distribuição aproximada à Normal pelo que foi utilizada estatística não paramétrica. A etiologia da DRC mais prevalente foi a hipertensão arterial essencial (50,4%) e a Diabetes *mellitus* tipo II (30,8%). A etiologia foi independente da idade e do sexo dos doentes.

Dos doentes incluídos, 48 doentes já estavam sob TSR com hemodiálise. Dos restantes 84 doentes, 3 estavam no estadio III, 46 doentes no estadio IV e 35 no estadio V da DRC. A hipertensão arterial essencial e a diabetes *mellitus* tipo II foram as comorbilidades mais prevalentes (93,2% e 47,0% respetivamente)

A permeabilidade primária às 48h foi de 91,7%; às 6 semanas foi de 88,6% e às 12 semanas foi de 80,3%. O sucesso da fístula às 6 semanas foi de 71,3% e às 12 semanas foi de 66,3%.

Não se verificaram associações estatisticamente significativas na análise univariada e bivariada entre as variáveis de caracterização demográfica, caracterização da doença renal crónica, comorbilidades e terapêutica antiagregante ou anticoagulante.

Na análise multivariada as características demográficas e clínicas não foram fatores de risco independentes para o sucesso das fístulas proximais às 6

semanas e às 12 semanas. A pressão arterial sistólica peri-operatória foi um fator preditor independente de permeabilidade às 48h. O diâmetro da veia com garrote foi fator preditor independente de sucesso das fístulas proximais às 6 semanas e às 12 semanas. Da análise de curvas ROC definiu-se uma área sob a curva igual ou superior a 0,7 para os três preditores. O *cut-off* otimizado para a pressão arterial sistólica peri-operatória foi de 154 mmHg; para o diâmetro da veia com garrote de 3.9 mm (para sucesso às 6 semanas e às 12 semanas) correspondendo índices de Youden entre 0.3 e 0.4.

DISCUSSÃO

Este estudo foi desenhado para avaliar o valor preditivo do mapeamento vascular pré-operatório no sucesso das fístulas arteriovenosas proximais.

Foram tidos em conta os mecanismos conhecidos que levam à falência/insucesso de uma FAV e as estratégias para controlo de viés e confundimento das variáveis e co-variáveis que se consideraram potencialmente envolvidos na associação entre as características anatómicas e hemodinâmicas do mapeamento pré-operatório e o sucesso da fístula.

Para controlo das variáveis de caracterização demográfica, caracterização da doença renal, comorbilidades e terapêutica antiagregante/anticoagulante, variantes anatómicas arteriais do membro superior e complicações cirúrgicas foram utilizadas a restrição, variáveis *proxi* e análise multivariada.

O facto de ser um estudo unicêntrico introduz um viés relacionado com a técnica cirúrgica e o cirurgião que a executa, muito embora o procedimento esteja protocolado e internacionalmente estabelecido. O viés de seleção relacionado com o facto de os doentes referenciados para FAV proximal como primeiro

acesso são aqueles cujos leitos vasculares do membro superior não são adequados para uma fístula distal não é possível ultrapassar com um estudo observacional. Tal colocaria em causa o princípio de *equipoise*.

A interpretação e representatividade dos resultados e conclusões devem ter em atenção estas considerações.

A permeabilidade primária e sucesso da fístula às 6 semanas e às 12 semanas está dentro do espectro de resultados descritos na literatura.

A permeabilidade às 48h e o sucesso às 6 semanas e às 12 semanas foram independentes das variáveis de caracterização demográfica, caracterização da doença renal, comorbilidades e terapêutica antiagregante e anticoagulante.

Na literatura muitos estudos definem a obesidade e a Diabetes (entre outros) como fatores de risco para trombose. Porém, a maioria desses estudos incluem diferentes tipos de fístula e têm definições heterogéneas de permeabilidade e sucesso.

Estes resultados sugerem que, a nível proximal os fatores hemodinâmicos locais se sobrepõem à influência deletéria de comorbilidades cardiometabólicas.

Em relação ao mapeamento pré-operatório, as características medidas da artéria (diâmetro e débito) foram independentes da permeabilidade e sucesso das fístulas nos períodos mencionados. Estes resultados podem ser explicados pelo espectro de resultados de diâmetro e fluxo da artéria umeral.

Pressão arterial imediatamente pré-operatória foi fator preditivo de permeabilidade às 48h. Apesar de ser um parâmetro com grande labilidade, a avaliação pré-operatória tem a vantagem de condicionar a decisão cirúrgica e adequar o *timing* da intervenção aos valores tensionais.

O diâmetro da veia com garrote foi o fator preditor mais consistente de sucesso da fístula às 6 semanas e às 12 semanas. Este é o aspeto mais importante deste estudo, mostrando a necessidade de protocolar a metodologia da avaliação pré-operatória e a técnica de avaliação da veia com garrote. Permite avaliar indiretamente a capacitância da veia e o seu calibre.

CONCLUSÕES:

A idade, sexo, etiologia, estadio da DRC e comorbilidades não foram fatores preditivos independentes de permeabilidade e sucesso precoce nas FAV proximais.

Pressão arterial sistólica imediatamente pré-operatória foi fator preditivo independente de sucesso para permeabilidade primária às 48h com um *cut-off* otimizado em 154mmHg.

Diâmetro da veia medido com garrote foi um fator preditor para o sucesso da FAV proximal às 6 semanas e às 12 semanas com um *cut-off* otimizado de 3.9mm.

ABBREVIATIONS AND ACRONYMS

The following abbreviations and acronyms were used:

95CI	95% Confidence Interval
AV_dist	Distance between brachial artery and superficial vein (cephalic or basilica).
AVF	Arterio-Venous Fistula
AVG	ArterioVenous Graft
BAD	Brachial Artery Diameter
BAF	Brachial Artery Flow
BAF6W	Brachial Artery Flow at Six Weeks
BAF12W	Brachial Artery Flow at twelve Weeks
BB	BrachioBasilic
BC	BrachioCephalic
BMI	Body Mass Index
CDUS	Colour Doppler Ultrasound
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
CV	Central Venous
DAG	Direct Acyclic Graph
DBP	Diastolic Blood Pressure
df	Degrees of Freedom
DMII	Type II *Diabetes Mellitus*
DOPPS	Dialysis Outcomes and Practice Patterns Study

dt_DMII	Time since diagnosis of type II *Diabetes mellitus*
dt_HT	Time since diagnosis of systemic hypertension
ESRD	End Stage Renal Disease
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
GOLD	Global Iniciative for Chronic Lung Disease
HD	Hemodialysis
HFF	Hospital Prof. Dr. Fernando Fonseca
HT	Arterial Hypertension
IH	Intimal Hyperplasia
IQR	Inter-Quartile Range
JSDT	Japanese Society Dialysis Treatment
KDOQI	Kidney Disease Outcomes Quality Initiative
KS	**Kolmogorov-Smirnov**
LBB	Left BrachioBasilic
LBC	Left BrachioCephalic
LL_anast	Latero-Lateral anastomosis
LT_anast	Latero-Terminal anastomosis
MAP	Mean Arterial blood Pressure
NYHA	New York Heart Association
OR	Odds Ratio
OT	Operation Theatre
PAD	Peripheral Arterial Disease
pmi	per million inhabitants
PNS	Portuguese Nephrology Society

PP	Pulse Pressure
PSV	Peak Systolic Velocity
PSV6W	Pico-Systolic Velocity at six Weeks
PSV12W	Pico-Systolic Velocity at twelve Weeks
Q1	Quartile one
Q3	Quartile three
RBB	Right BrachioBasilic
RBC	Right BrachioCephalic
RCAVF	Radio-Cephalic Arterio-Venous Fistula
RCT	Randomized Controlled Trials
RI	Resistance Index
RI6W	Resistance Index at six Weeks
RI12W	Resistance Index at twelve Weeks
ROC	Receiver Operative Characteristics
RR	Relative Risk
RRT	Renal Replacement Therapy
SBP	Systolic Blood Pressure
Sens	Sensitivity
Specif	Specificity
TAVmean	Time Average mean Velocity
US	United States
USRDS	United States Renal Data System
VAS	Vascular Access Society
VD_diff	Difference between vein diameter with tourniquet and vein diameter without tourniquet

VD_ratio	Ratio between vein diameter with tourniquet and vein diameter without tourniquet
VD6W	Vein Diameter at six Weeks
VD12W	Vein Diameter at twelve Weeks
VDT	Vein Diameter with Tourniquet
VDWT	Vein Diameter without Tourniquet
YI	Youden Index

INTRODUCTION

INTRODUCTION

Epidemiology data on end stage renal disease and hemodialysis

End stage renal disease (ESRD) is increasing worldwide and is estimated to further increase in the next 10 years. According to the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) registry [1] which describes the epidemiology of renal replacement therapy (RRT) for ESRD within Europe via the national and regional renal registries, 70 953 individuals started RRT for ESRD in 2014, which equated to an overall unadjusted incidence rate of 133 per million inhabitants (pmi). The unadjusted incidence rate was highest in Portugal (237 pmi), Greece (218 pmi) and Cyprus (204 pmi). Regarding RRT prevalence, 490 743 individuals were receiving RRT for ESRD in 2014. This equated to an unadjusted prevalence of 924 pmi and Portugal had the highest unadjusted prevalence rate (1 794 pmi) [1].

According to the Portuguese Nephrology Society (PNS) registry, 11 738 patients were under RRT with hemodialysis (HD) in 2016, which represents nearly 60% of all RRT patients in Portugal in 2016. Among these, 2 166 were new patients (90% of all new patients in RRT in 2016) which represents an incidence rate of 209.11 pmi. This represents an increase of almost 40% in incidence rate in 20 years [2].

Background on vascular access for hemodialysis – guidelines and economic burden

From a technical point a view, a reliable vascular access is essential for the survival of patients with ESRD undergoing HD.

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, the Japanese Society for Dialysis Treatment (JSDT) and the Vascular Access Society (VAS) guideline 3 all state that autogenous arteriovenous fistula (AVF), as distal as possible in the non-dominant upper limb, is the access of choice [3-6]. However, poor vascular bed limits options to proximal access or even vascular grafts [7], and even autogenous AVF have a 10-37% early thrombosis rate [8-10].

These same societies unanimously state that patients who have opted for HD should start a dialysis program with a functioning vascular access and ideally should be early referred to the vascular access team [8-10].

According to PNS 2016 registry, 83.9% of HD patients in 2016 had a functional AVF or graft (AVG). However, only 45.6% of patients had a reliable AVF or AVG in the first HD session. These numbers did not significantly change since 2008 and present a marked geographic heterogeneity in Portugal [2]. According to the US Renal Data System 2015 Annual Data Report [11] in the United States of America (USA) 80.2% of patients were using a catheter at HD initiation in 2013, which has changed little since 2005. By December 2013, 62.5% of prevalent dialysis patients were using an AVF. At 1 year after HD initiation, 80% of patients were using either an AVF or AVG without the presence of a catheter.

The field of vascular access surgery is unrewarding and doomed to failure. Its purpose is to delay downfall as long as possible and to minimize morbidity associated with multiple admissions and multiple procedures in patients with a heavy load of comorbidities.

Dysfunction or related vascular access complications account for 20-30% of hospital admissions among this population, resulting in high morbidity, high

mortality and high economic burden [12, 13]. According to Medicare data, in the USA approximately one-half of Medicare's ESRD budget (over 6 billion dollars in 1991) were spent on ESRD related morbidity and associated hospitalizations. Of these, 15% were directly related to vascular access surgical complications or dysfunction [14, 15]. According to conservative estimations, 7 500 US dollars were spent per hospital stay, which means that in 1995, 675 million dollars (nearly 10% of the ESRD budget) were spent on vascular access dysfunction or surgical complications, and it is assumed that this is a gross underestimate analysis of the total cost for vascular access-related morbidity. In 2001, vascular access composed 7.5% of the 14 billion US dollars spent by Medicare on the ESRD program (approximately $1 billion per annum) [12].

Vascular access failure results in the loss of vascular capital, reducing potential sites for future accesses and, in more severe cases, conditioning the patient to a less desirable alternative such as a long-term central venous access with higher mortality and morbidity due to infection and thrombosis [16].

Prediction models based on clinical and color Doppler ultrasound (CDUS) would be a simple, fast and affordable way to determine the best access for each patient, and would prevent unsuccessful surgical procedures and morbidity associated with progressive ESRD in patients with non-functional AVF.

Preoperative Doppler ultrasound for vascular mapping – evidence available

Although the role of Doppler ultrasound has been progressively established in the last decade as a complement to pre-operative assessment and follow-up, it is still not consensual [4, 17, 18]. Physical examination and CDUS are recommended for pre-operative vascular mapping according to KDOQI, JSDT and VAS

guidelines [3, 4, 6] with the rationale that it could overcome the gap that physical examination alone leaves in many patients [19].

However, the quality of evidence and level of recommendation are far from perfect: the 2006 KDOQI guidelines considered a physical examination and CDUS for pre-operative evaluation as a type B recommendation (it was recommended that clinicians routinely followed the guideline for eligible patients and there was a moderately strong evidence that the practice improves health outcomes); the 2011 JSDT guidelines recommend the pre-operative evaluation through physical examination (level 1) although “the true effect may be substantially different from the estimate of the effect” (quality of evidence level C). CDUS is “preferred” (recommendation level 2) in case the type of VA and location cannot be determined by visual examination or palpation of the vessels (quality of evidence level B - the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different). The Vascular Access Society recommends pre-operative CDUS and considers it as a level II evidence, based on one 2001 study where patients were randomized to physical examination only or physical examination and CDUS. AVF failure rate was 25% when pre-operative assessment depended on physical examination alone, compared with 6% ($p<0.002$) when ultrasonography was used [6, 20].

Two other randomized controlled trials (RCT) [21, 22] were analysed in a systematic review and there were more successful fistulas in the duplex group (pooled odds ratio 1.96; 95% confidence interval 0.85-4.50). This result did not reach statistical significance. Heterogeneity between CDUS protocols was an important limitation in this study [23]. After these RCTs, the only clinical trial registered as completed failed to demonstrate higher patency rates when routine

vs. selective pre-operative CDUS was performed [18]. However, the study was designed to detect a 27% effect difference between groups and a 15% difference was observed which means that the sample size was underpowered [18].

During the last decades, ultrasound has been recognized as a powerful diagnostic and percutaneous procedure guided tool with widespread applications in health care. It is safe, non-invasive, devoid of ionizing radiation, does not use kidney injury intravenous contrast agents and is readily available and inexpensive. It allows for non-invasive real-time evaluation of both structural and functional aspects of the vessels. An always cited disadvantage is related to the inter-observer variability according to the ultrasound technique and radiologist expertise [24]. Particularly in upper limb vascular mapping, a major limitation is its relative inability to assess central vein patency so that contrast venography may still be needed if a central venous stenosis or occlusion is suspected [24]. Many other factors must be kept in mind when measuring vessels' diameter and blood flow: the diameter of an artery may vary as much as 20% during the cardiac cycle; errors associated to the vessel area measurement may be as high as 20% for a 10mm vessel and even higher for smaller vessels such as the brachial artery or the cephalic vein; volumetric flow is difficult, as it is frequently associated with errors of 20% to 100% due to pulsatile cardiac cycle; and complex heterogeneous patterns of velocity, namely near bifurcations such as in the brachial artery in the lower third of the arm, lead to inaccurate angle estimation [25-29]. However, the literature is scarce regarding accurate data on errors in clinical practice. One study conducted in our department, where the precision of CDUS for vascular mapping was tested in healthy volunteers, showed that the cephalic vein diameter and brachial artery diameter and flow in the lower third of the arm were not

statistically different in three CDUS evaluations performed by the same dedicated radiologist, each one week apart (submitted) [30].

A further step in CDUS pre-operative vascular mapping in vascular access for HD is related to the need of protocols for surgical decision making. It is easy to decide to use a vein and an artery in a young patient with no comorbidities with a 4mm cephalic vein and a pulsatile non-calcified artery with a 0.05L/min blood flow. It is easy to decide not to use an artery or a vein when it is very small, calcified, with low flow in an old patient with cardiovascular comorbidities. However, in patients not belonging to one of these groups, surgical decision is complicated.

Several studies support the 2.0 to 2.5mm vein diameter as the threshold for successful creation of a fistula [31, 32]. Radiocephalic fistulae (RCAVF) constructed in veins less than 2.0mm in diameter had only a 16% primary patency at 3 months compared with 76% for those with veins greater than 2.0mm [32].

A pre-operative arterial diameter less than 1.6mm has been associated with a high failure rate in RCAVF [33, 34]. Other authors compared the 2.0mm arterial diameter threshold suggesting that a minimum diameter of 2.0mm is required for successful fistula creation [31]. Successful RCAVF has been described with a pre-operatively measured radial artery diameter of 2.7mm vs 1.9mm in failed RCAVFs and with a diameter higher than 1.5mm vs 1.5mm or less immediate patency rate. In the higher than 1.5mm group success was 92% vs 45% in the less than 1.5mm group [35].

European guidelines suggest that the minimum diameter of the radial artery should be at least 2.00mm for AVF surgery [6].

However, most of these studies are observational retrospective studies or historical cohorts [31, 36]. Only one prospective study aimed to predict primary patency in primary RCAVD where receiver operating characteristic (ROC) curves analysis defined the limits of variables relevant for distal AVF success (vein diameter >1.8mm, artery diameter >1.6mm, vein distensibility >0.4) [37].

No prospective studies were found aiming at predicting primary patency of primary brachiocephalic (BC) AVF based on clinical and CDUS variables.

Vascular dynamics including AVF patency is complex, multifactorial and polygenic and many other CDUS anatomical and hemodynamic parameters have been associated with AVF patency. The predictive value of the radial artery peak systolic velocity (PSV) and resistance index (RI), calculated from pre-operative ultrasonography parameters, is uncertain [34, 38, 39]. The cephalic vein diameter increase after application of a proximal tourniquet is an important predictor of success. In a group of successfully created AV fistulae, the vein diameter increased by 48%, while vein diameter only increased by 11.8% in the group of failed AV fistulae [40].

A major gap in establishing that routinely pre-operative CDUS is recommended and establishing the parameters and thresholds for surgical decision making is standardization of CDUS evaluation setting and protocol. There is no generally accepted “standard” procedure for what is vascular mapping. The arterial evaluation should include arterial patency, diameter and blood flow and the presence of arterial calcification. Venous evaluation should include diameter continuity with the proximal central veins, and absence of obstruction. The central veins should be indirectly assessed [19]. Anatomic variations should be highlighted since high bifurcation of the brachial artery may occur in 20% of

patients and absence, duplication or drainage variations of superficial veins are not uncommon. In the methods section, the pre-operative CDUS vascular mapping is described [19, 41, 42].

The major goal of pre-operative vascular mapping is to aid on surgical decision making in patients with vessels with borderline features, which cannot be immediately discarded but are not optimal for AVF construction. Those represent most patients referred to AVF construction. These borderline vessels are probably also the most vulnerable to effect interaction of clinical factors and comorbidities, making the puzzle even more complex where the same diameter vein might be suitable for AVF construction in a young patient with no comorbidities and not suitable in an older patient with cardiovascular comorbidities.

Clinical risk factors for vascular access – evidence available

Demographic and clinical factors have been inconsistently predictive of AVF success. The quality of the evidence has the previous stated limitations where the majority of studies are observational and retrospective studies.

Patients **older than 65 years** have been associated to poor AVF success compared to younger patients. This was explained by the decreased vascular compliance and likelihood of having cardiovascular comorbidities [43]. **Female gender** has also been associated with poor fistula outcomes [44, 45]. Differences in vessel diameters and compliance as well as differences in vascular reactivity and platelet aggregation after vascular injury have been proposed to explain these differences [44, 45]. **Diabetes *Mellitus* and hypertension** due to vascular damage with calcification and stiffness, with reduction of blood flow, narrow

lumen and lack of compliance are frequently associated with worse outcomes after AVF [44-47]. **Obesity** has also been suggested to compromise fistula creation and maturation [48]. Physical examinations becomes harder and less accurate, and narrowing of the brachial and/or axillary veins with hemodynamic effects have also been described [49]. The surgical procedure is technically more difficult and more prone to surgical complications. Finally, obesity, hypertension and diabetes *mellitus* covariate with each other.

Predictors of vascular access success – the gap knowledge

The usefulness of pre-operative CDUS and the anatomic and hemodynamic CDUS parameters required for AVF success are still lacking quality evidence. Major vascular access and dialysis society's guidelines are outdated and do not take into account at least the last 5 years of evidence [3, 4, 6]. Pre-operative CDUS protocols are not standardized across centres. Which anatomical and hemodynamic features should be taken into account and which thresholds should be considered according to AVF location are based on observational inconsistent data. How do clinical features interact with CDUS parameters to predict AVF success? An AVF success is defined as a matured AVF suitable for HD needle cannulation. **Maturation** is the remodelling process whereby the AVF drainage vein enlarges its wall and lumen due to histological changes (vein arterialization). It should have a diameter of 6mm, be less than 6mm below the skin surface and have a flow rate greater than 600 ml/min [50]. Shear stress stimulates endothelial cells and triggers intracellular signalling pathways modulating gene expression [51-53]. Remodelling in maturing AVFs is primarily characterised by eccentric medial hypertrophy resulting from increased circumferential tension [54] .

Significant remodeling occurs within 4–6 weeks post formation with increases in flow and lumen area. After this, flow rate reduces until remodeling becomes quiescent which may take 3–8 months post formation [55-58].

One study showed that the functional maturation rate of AVFs decreased from 73% to 57% as the AVF creation rate increased from 61% to 73% after routinely pre-operative assessment with CDUS. The authors suggested that one possible explanation was that selection criteria based on findings at pre-operative imaging needs further refinement [59].

Evaluating vascular characteristics pre-operatively, with *Doppler* ultrasound, selecting the best procedure for each patient, is a step towards maximizing AVF success. Taken together, one can understand why pre-operative CUDS is a hot topic in HD vascular access clinical science.

AIM

The aim of this thesis was to evaluate pre-operatively upper limb anatomical and hemodynamic parameters measured by CDUS as predictors of brachiocephalic and brachiobasilic (BB) AVF success and how they interact with demographics and comorbidities for AVF success.

Primary aim

To evaluate the predictive value and thresholds of anatomical and hemodynamic CDUS-derived parameters of brachial artery, cephalic vein and basilic vein for brachiocephalic and brachiobasilic AVF success.

Secondary aim

To evaluate the effect interaction of pre-operatively upper limb anatomical and hemodynamic CDUS-derived parameters and clinical and demographic features for brachiocephalic and brachiobasilic AVF success.

INSTITUCIONAL SETTING

Hospital Professor Doutor Fernando Fonseca (HFF) is located in Amadora, Portugal. It serves a population of 600 000 people, the majority of which are underprivileged.

It is a Teaching Hospital for Medical Students and is accredited by the Portuguese Medical Board for General Surgery Residency. Vascular access surgery is performed at HFF since 1996.

The Hospital has a Nephrology department with peritoneal dialysis and a HD center which works together with the dialysis centers in the surrounding cities. According to the Portuguese Law Despacho n.º 47-A/2011 published in *Diário da República, 2.ª série — N.º 1 — 3 de Janeiro de 2011*, Hospitals included in the National Health Services network are responsible for the first definitive vascular access for HD.

In 2010 a Vascular Access Unit, with dedicated surgeons, radiologists and nephrologists, was created at HFF. Since then, more than 120 vascular access surgeries have been performed each year.

Patients are **referred** to vascular access surgery from the Nephrology department.

Chronic kidney disease (CKD) patients are evaluated in an appointment with the nephrologist to decide the best **option for chronic RRT** (HD or peritoneal dialysis are performed at HFF).

A **pre-operative CDUS vascular mapping** is performed to every patient referred for chronic HD. CDUS is performed by a dedicated radiologist with 20 years'

experience in *Doppler* ultrasound and more than 5 years in upper limb vascular mapping.

After vascular mapping, clinical cases are presented in a weekly **multidisciplinary meeting** where nephrologists (including interventional nephrologists), surgeons dedicated to vascular access surgery and the dedicated radiologist are present to decide the best option for each patient.

Besides the type of vascular access, according to patients' clinical condition, a priority is set where "HD1" patients are those under HD with immediate priority and 1, 2 and 3 CKD patients under conservative therapy with decreased level of priorities (1 month, up to 3 months and more than 3 months to vascular access construction).

The author works in the HFF surgical department as a hospital assistant in general surgery and is one of the dedicated vascular access surgeons since 2010.

From a scientific point of view, HFF vascular access unit has a special interest in the study of CDUS-derived parameters as predictors of AVF maturation and patency. Previous results from our unit have been presented in international meetings regarding the prevalence of anatomic variants (higher than 35%) and how they were associated with arteriovenous fistula failure [60, 61]. Retrospective analysis of our proximal AVF as first vascular access was associated with higher brachial artery flow, higher peak systolic velocity of brachial artery, and higher distance between artery and vein, with patency at one year being currently assessed. Also, a study on CDUS vascular mapping protocol and prospective evaluation of CDUS vascular mapping precision in healthy volunteers has been submitted [30].

METHODS

METHODS

Study design

Observational, analytical, longitudinal study with prospective data collection.

Inclusion criteria

Adult patients, referred for construction of brachiocephalic or brachiobasilic AVF who provided written informed consent to participate in this study.

Exclusion criteria:

- Patients with no available pre-operative CDUS vascular mapping;
- Patients with anatomical arterial variants specifically high brachial artery bifurcation;
- Patients with previous ipsilateral definitive vascular access.
- Patients needing AVF surgical revision.

Outcomes

Patency at 48h post-procedure was clinically evaluated by the assistant surgeon or nephrologist, defined as the presence of a palpable thrill and continuous murmur over the AVF venous trajectory during the first 48 hours.

Patency at 6 weeks and 12 weeks post-procedure was measured by CDUS. AVF success at 6 weeks and 12 weeks was measured by CDUS and defined as a vein diameter of at least 6 mm and a AVF flow of at least 600mL/min.

Sample size calculation

Considering the assumptions:

- longitudinal study;

- Type I error of 5% and type II error of 80%;

- According to submitted data from our center and in accordance to literature, a 30% of AVF failure at 3 months was considered for sample size calculation [8-10];

- multivariate model analysis with no more than 4 independent variables;

- 10% of drop-outs.

According to *Peduzzi* et. al. [62] **160 is the minimum number of cases to include in the study** (being 134 the minimum number of participants required at the end of the study).

Peduzzi et. al. [62] defines the sample size for logistic regression (N) as the quotient of 10k and p (N=10k/p). p is the smallest of the proportions of negative or positive cases in the population and k the number of covariates/ independent variables.

Methods used for bias and confounding assessment and control

1 – Standard approach: According to literature review. Variables that might influence the AVF success not directly through CDUS-derived parameters were listed (Annex A).

2 – Direct acyclic graph: common effects might represent confounding and common causes might represent bias (Figure 1).

A third approach for confounding is multivariate analysis which is described in the statistical analysis section.

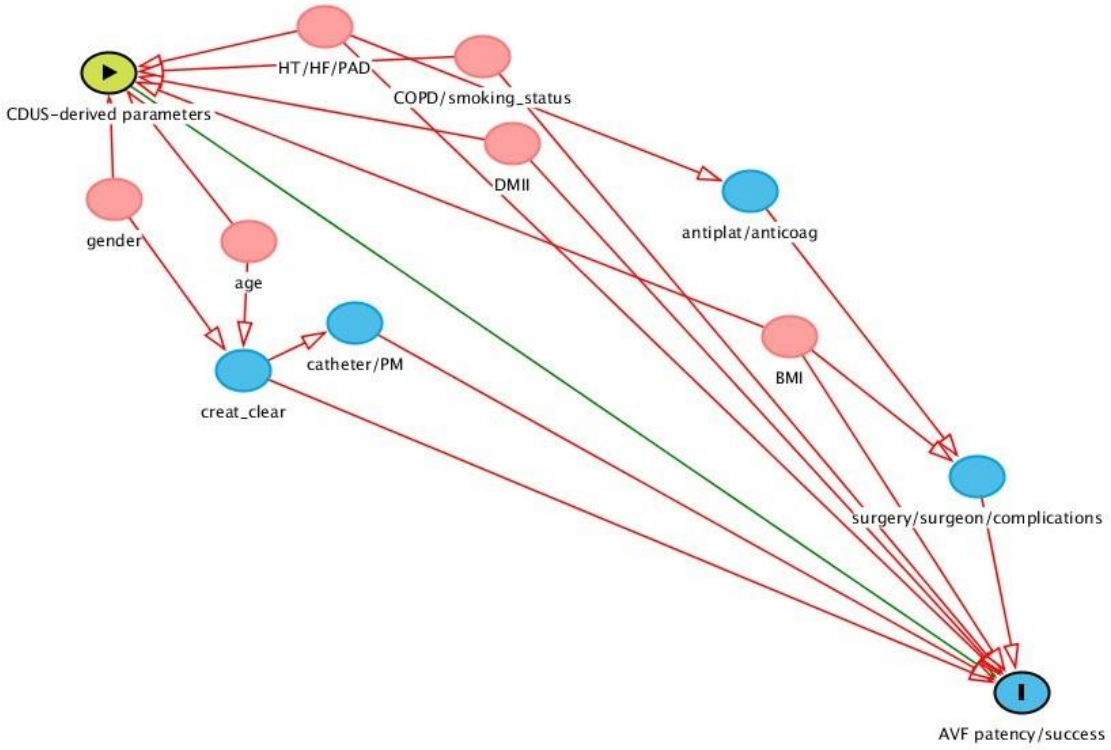


Figure 1 – Direct Acyclic Graph. Green color – exposure variable. I – outcome variable.

Variables measured and definitions

Patients' demographics and clinical factors:

Gender and age in years. Systemic arterial hypertension (HT), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), type II Diabetes Mellitus (DMII), anti-platelet and/or anticoagulant therapy previously to the procedure.

Patients' clinical variables were assessed by clinical interview immediately before the surgical procedure. Clinical interview was performed by the investigator.

HT was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or if the patient is taking antihypertensive medication, or if the subject was told on 2 occasions that he or she had hypertension [63]. It was measured as a binary variable (present or absent). If present, the time in years after the diagnosis was recorded.

HF was measured as a binary variable (present or absent). If present, the New York Heart Association (NYHA) scale for heart failure was recorded [64].

COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 recommendations as persistent signs and symptoms of respiratory and airglow limitation, namely chronic productive cough for three months in each of two successive years in a patient with no other causes of chronic cough [65].

COPD was measured as a binary variable (present or absent). If present, the time in years after the diagnosis was recorded.

Smoking status was defined as smoker, previous smoker or never-smoker.

Peripheral artery disease was classified according to Fontaine classification (grade I – asymptomatic; grade II – intermittent claudication; grade III – ischemic rest pain; grade IV – ulceration or gangrene) [66].

Body mass index (BMI) was measured as weight (kg) / height^2 (m).

DMII was defined as according to the American Diabetes Association criteria (hemoglobin A1c level of 6.5% or higher, a fasting plasma glucose level of 126 mg/dl or higher; a 2-hour plasma glucose level of 200 mg/dl or higher during a 75-g oral glucose tolerance test or a random plasma glucose of 200 mg/dl or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis)[67]. DMII was measured as a binary variable (present or absent). If

present, the time in years after the diagnosis and if insulin was part of chronic medication or not was recorded.

Anti-platelet and/or anticoagulant therapy was measured as a binary variable (present or absent).

CKD etiology, presence/absence and location of pace-makers, cardiac implanted defibrillators, central venous lines and/or dialysis catheters have been recorded.

CDUS-derived parameters:

- brachial artery diameter (BAD) (mm),
- brachial artery flow (BAF) (L/min),
- cephalic or basilic vein diameter (mm) measured with and without tourniquet (VDT and VDWT, respectively) (mm),
- venous compliance (calculated as the module of VDT-VDWT and the quotient VDT/VDWT).
- venous to artery distance (mm)

Intra-operative arterial systolic and diastolic blood pressure (SBP and DBP, respectively) *(mmHg)*, were measured immediately at the beginning of the procedure in the ipsilateral arm, with the patient lying down on the operating table before local anesthesia was performed. Pulse pressure (PP) and mean arterial pressure (MAP) were calculated as PP=SBP-DBP and MAP=1/3SBP+2/3DBP respectively [68].

Surgical procedure: Surgical team, type of anastomosis (side-to-side or end-to-side anastomosis) and surgical complications were recorded. Surgical protocol is described in the following section.

Color Doppler Ultrasound Protocols

Patients fatigue or exercise, room temperature, equipment and radiologist experience might introduce bias and confounding.

A standardized CDUS protocol has been established and included a dedicated radiologist, specific equipment, controlled room temperature between 22ºC-24ºC and a 10 minutes resting period for the patients in the waiting room. This aims to avoid interference due to vasodilation after walking to the department.

Pre-operative CDUS vascular mapping protocol

B-mode, together with colour and pulsed DU is performed using an ultrasound scanner *Toshiba Applio* equipped with a high frequency Doppler dedicated transducer (PLT-704AT, 5-11 MHz). When necessary, namely in thick or oedematous patients, or for the evaluation of the subclavian vessels, a convex transducer is used (PVT- 375NT, 2.5-6 MHz)

The examination is performed with the patient in the seated position, with the non-dominant arm resting in a pillow, in the ipsilateral hip, with the palm of the hand facing up.

A systematic approach is performed, encompassing the arteries, deep vein system and superficial vein system.

We usually start with the evaluation of central vessels. Subclavian and axillary vessels are assessed for direct and indirect signs of central occlusion (vein) and anatomical variants (artery and vein).

Afterwards, a tourniquet is placed in the proximal upper arm so that superficial veins flow, but not the brachial artery flow are occluded.

Cephalic vein patency and diameter are measured at the wrist, forearm and at the upper arm. The vein is followed, in the transverse plane, until the point of confluence with the axillary or subclavian vein. The classical cephalic-axillary confluent is at the highest portion of the delto-pectoral groove, the *fosseta* of Morhenheim or sub-clavicular *fosseta* of Gerdy [69]. Anatomical variants, strictures and large collaterals are noted.

The basilic is the largest superficial vein in the arm, also known as the royal vein. Basilic vein diameter and the level of its confluence with the deep system is assessed in the upper arm. The confluence occurs at inconstant levels, ranging from low brachial veins to the axillary or subclavian vein [69].

Special care is taken on the pressure applied with the probe, during veins' assessment, so as not to collapse these superficial structures.

The tourniquet is subsequently removed.

Brachial artery, radial artery and cubital artery are assessed for anatomic variants, presence of atheromatous calcifications, possible occlusion/aneurism, patent lumen diameter and blood flow.

Blood flow is calculated with the equipment built-in system software, that uses the formula:

$$Flow\ rate\ (ml/min) = TAV_{mean}(cm/s) \times area\ (cm^2) \times 60$$

where TAV_{mean} is time average mean velocity.

The Doppler sample volume is set to fit the entire diameter of the vessel, and the Doppler angle is kept as low as possible, to avoid measurement errors.

The deep veins' patency is evaluated together with the arteries.

Cephalic vein at the forearm and upper arm, and basilic vein are finally assessed for lumen diameter without tourniquet.

If for any reason a cephalic vein at wrist, forearm or upper arm is not suitable for AVF surgery (due to its narrow diameter, peripheral or central thrombosis or anatomic variant of central or peripheral arteries and/or veins) the opposite arm is assessed according to the systematic approach previously described.

CDUS data is recorded in the patients' digital clinical file (Appendix A).

CDUS arterio-venous fistula follow-up protocol

CDUS AVF follow-up was at 6 weeks and 12 weeks after surgery (48h assessment is based on clinical criteria only – presence of continuous thrill and bruit assessed by the assistant vascular access surgeon and principal investigator).

The same setting and systematic approach is applied as previously described for pre-operative vascular mapping.

We usually start with the evaluation of central vessels. Subclavian and axillary vessels are assessed for direct and indirect signs of central occlusion (vein) and anatomical variants (artery and vein).

No tourniquet is placed.

Cephalic and basilica vein patency and diameter are measured at the wrist and at the upper arm according to the previously described technique.

Brachial artery, radial artery and cubital artery are assessed for anatomic variants, presence of atheromatous calcifications, possible occlusion/aneurism, patent lumen diameter, blood flow, peak systolic velocity and resistance index as previously described. The Doppler sample volume is set to fit the entire diameter of the vessel, and the Doppler angle is kept as low as possible, to avoid measurement errors.

Brachial artery diameter, blood flow, peak systolic velocity and resistance index are measured with the equipment built-in system software. Arteriovenous anastomosis diameter is measured.

The arterialized vein (cephalic or basilica vein) patency and diameter is measured at the upper arm. The vein is followed, in the transverse plane, till the confluence with the brachial, axillary or subclavian vein. Distance to the skin (in mm) and longitudinal superficial length (in cm) is recorded. Anatomical variants, strictures and large collaterals are noted.

Data is recorded on patients' digital clinical file (Appendix B).

Brachiocephalic and Brachiobasilic Arterio-Venous Fistula Surgical Protocol

Surgical procedures were performed by the same surgical team and according to the surgical protocol described below.

The patient is admitted to the outpatient clinic two hours before surgery.

Patients under chronic HD program do not perform AVF surgery in the same day in which dialysis is scheduled. Patients fast for at least three hours. Systolic blood pressure lower than 100mmHg at the first measurement is a contra-indication for the surgical procedure. Anticoagulant therapy is discontinued or a bridge period with low molecular weight heparin is performed according to the nephrology

medical assistant recommendations. Other medical therapy including anti-platelet agents are not discontinued.

After confirming consent for the surgical intervention and the surgical site, patients are given 50 mg of hydroxyzine *per os*. A peripheral venous catheter is placed.

The operating room (OR) is fully equipped with non-invasive and invasive cardiorespiratory monitoring, mechanic ventilation, instrument and materials table and electronic equipment.

One principal surgeon, an assistant surgeon, a nurse and an assistant nurse constitute the OR team. The principal surgeon is one of the dedicated vascular access surgeons of the surgery department. Before and after the patient enters the OR, the safety check-list is performed by the OR team.

The patient is placed in the supine position with his/her selected surgical site arm abducted at a 90° angle to the body, and the other arm alongside his body.

The skin is prepared with a chlorhexidine-based preparation solution and the surgical drapes are placed.

The procedure is well tolerated under local anesthesia with ten to fifteen ml of a mixture of lidocaine 2% and ropivacaine 7.5%.

A three to four centimeters curved incision is made in the anterior aspect of the elbow, according to the pre-operative CDUS vascular mapping, namely the selected vein and distance between the vein and the artery.

Dissection begins with identification, exposure and isolation of the pre-operative selected vein. Only in rare occasions, when the pre-operative findings do not match the intra-operative findings, the other vein is explored.

The vein is tested for patency and distention with injection of twenty milliliters of heparinized (five thousand units diluted in one hundred milliliters of saline solution) saline solution.

If the vein is considered suitable, the brachial artery is then dissected, exposed and heparinized with twenty milliliters of the above mentioned solution, both proximally and distally.

A four to six mm arteriotomy and venotomy is performed and an arteriovenous anastomosis using a non-absorbable monofilament 6/0 suture (Prolene®) is fashioned. If using the cephalic vein, a terminal to lateral anastomosis is done, and in case of the basilic vein, a lateral to lateral anastomosis with distal vein ligation is performed.

Generally, a palpable thrill in the outflow vein is evident after the anastomosis. Proximal mobilization of the outflow vein is done to ensure extrinsic compression of the vein.

The surgical site in checked for bleeding and wound in close non-absorbable monofilament 3/0 suture (Nylon®).

Generally, the procedure is uneventful and the patient is discharged one hour after surgery with post-operative recommendations and pain medication. If for some reason the patient cannot be discharged he/she is admitted to the surgical department ward.

There is a scheduled post-operative visit at the second post-operative day, to check for surgical wound, complications and AVF patency.

Missing data

Missing data were considered as completely at random. No missing data imputation was performed. Missing data were excluded listwise for independent sample analysis and pairwise for paired sample analysis.

Ethical considerations

The study has been conducted according to the tenets of the Declaration of Helsinki in its latest amendment [70]. All participants signed the written informed consent for surgical/interventional procedures (form HFFEPE-MOD.016/t.DC/V6 reviewed in 2014) and informed consent for participating in this study (Appendices C and D), which was signed at the hospital admission or during follow up period.

The investigation protocol and the informed consent form were submitted and approved by the Ethics Committee of Hospital Prof. Doutor Fernando Fonseca and the Lisbon Medical School (Appendixes C-E).

This was an observational study and patients were treated according to the standard of care.

Statistical analysis

Parametric statistics **assumptions** were tested. When assumptions were not met, non-parametric statistical methods was used. For continuous variables, Gaussian distribution was assessed using the Kolmogorov-Smirnov test.

For **univariate analysis** of continuous variables between the study groups t-student for independent samples or Mann-Whitney tests were used. For nominal variables, a qui-square or a Fisher exact test was used. For comparison between

6 week follow-up and 12 week follow-up CDUS, t-student for paired samples or Wilcoxon test were used.

Logistic regression models with patency at 48 hours, 6 weeks AVF success and 12 weeks AVF success as dependent variables were performed.

Independent variables included those that were statistically significant in the univariate analysis and those that were biologically plausible (those that, according to the literature, would have a physiological reason to influence the AVF outcome even if not statistically significant in the univariate analysis).

Effect interaction between demographics/comorbidities and CDUS parameters were tested and included in multivariate regression models.

A maximum of four independent variables per model were considered according to the power calculation.

Receiver Operating Characteristic (ROC) curves were performed for statistical significant variables, as well as their Youden index and respective cut-off values.

Statistical significance was considered for an alpha<0.05.

RESULTS

RESULTS

Eligible sample

Between January 2016 and June 2017, 160 patients referred for brachiocephalic or brachiobasilic AVF surgery were screened. 132 were eligible, median age of 71 years old, ranging between 18 and 88 years old. 69.2% were male.

Figure 2 shows the reasons for exclusion: 13 patients were lost to follow-up before the 6 week follow-up CDUS; 5 patients died after surgery and before the 6 week follow-up period; 4 patients had high subclavian/axillar/brachial artery bifurcation; 2 patients needed AVF ligation due to surgical complications (steel syndrome); 1 patient did not perform pre-operative CDUS; 1 patient had a previous vascular access in the ipsilateral arm.

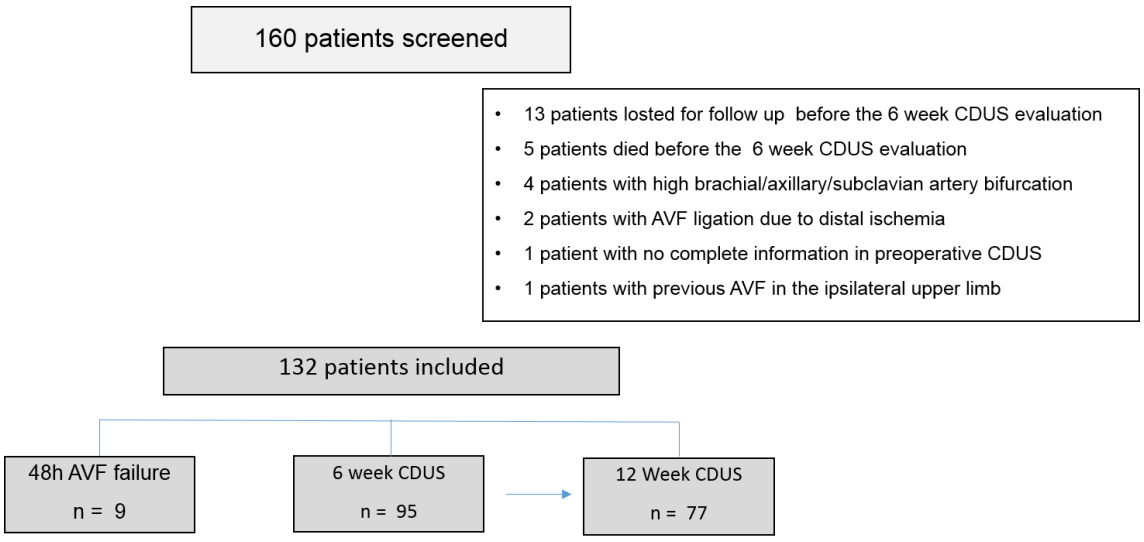


Figure 2 – Summary of patient selection and evaluation.

Descriptive statistics

Due to non-Gaussian distribution of several continuous variables, non-parametric statistics were used (table 1).

Table 1: Kolmogorov-Smirnov test for Gaussian distribution of continuous variables.

Variable	KS p-value	Variable	KS p-value	Variable	KS p-value
Age	**0.011***	VD_ratio	0.059	BAF6W	0.340
CrCl	0.187	AV_dist	0.597	PSV6W	0.160
BMI	0.828	BAF	0.571	RI6W	**<0.001***
dt_HT	**0.025***	BAD	**0.032***	VD6W	**<0.001***
dt_DMII	**<0.001***	SBP	0.756	BAF12W	**0.019***
VDT	0.183	DBP	0.707	PSV12W	0.006
VDWT	**0.024***	PP	0.758	RI12W	0.293
VD_diff	0.090	MAP	0.613	VD12W	**0.001***

KS – Kolmogorov-Smirnov; CrCl – Creatinine clearance; dt_HT – time since diagnosis of HT; dt_DMII – time since diagnosis of DMII; VDT – Vein Diameter with Tourniquet; VDWT – Vein Diameter Without Tourniquet; VD_diff = VDWT-VDT; VD_ratio = VDWT/VDT; AV_dist – Distance between brachial artery and cephalic/basilica vein; BAF – Brachial artery flow; BAD – Brachial Artery Diameter; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; PP – Pulse Pressure; MBP – Mean Blood Pressure; BAF6W – Brachial Artery Flow at Six Weeks. PSV6W – 6 Weeks Pico-Systolic Velocity; RI6W – 6 Weeks Resistance Index; VD6W – 6 Weeks Vein Diameter; BAF12W – Brachial Artery Flow at 12 weeks; PSV12W – 12 Weeks Pico-Systolic Velocity; RI12W – 12 weeks Resistance Index; VD12W – 12 Weeks Vein Diameter;

Age ranged between 18-88 years with a median of 71 years and an interquartile range (IQR) of 13 years. The histogram (Figure 3) is bell shaped although asymmetric.

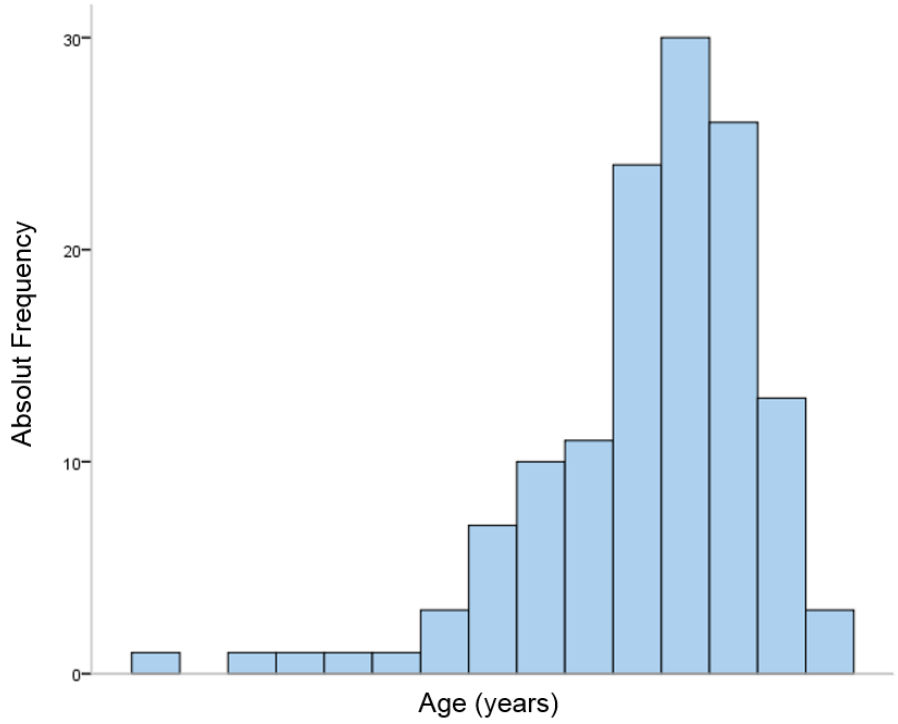


Figure 3 – Histogram of age distribution

Gender

69.2% (n=92) of the participants were male. Distribution of age was independent of gender: median of 71 years with an IQR of 12 years in males compared with a median of 71 years with an IQR of 15 in female patients (Figure 4) (Mann-Whitney mean rank of 66.19 and sum of ranks of 6023.0 for males and mean rank of 67.20 and sum of ranks of 2755.0 for females; p=0.888).

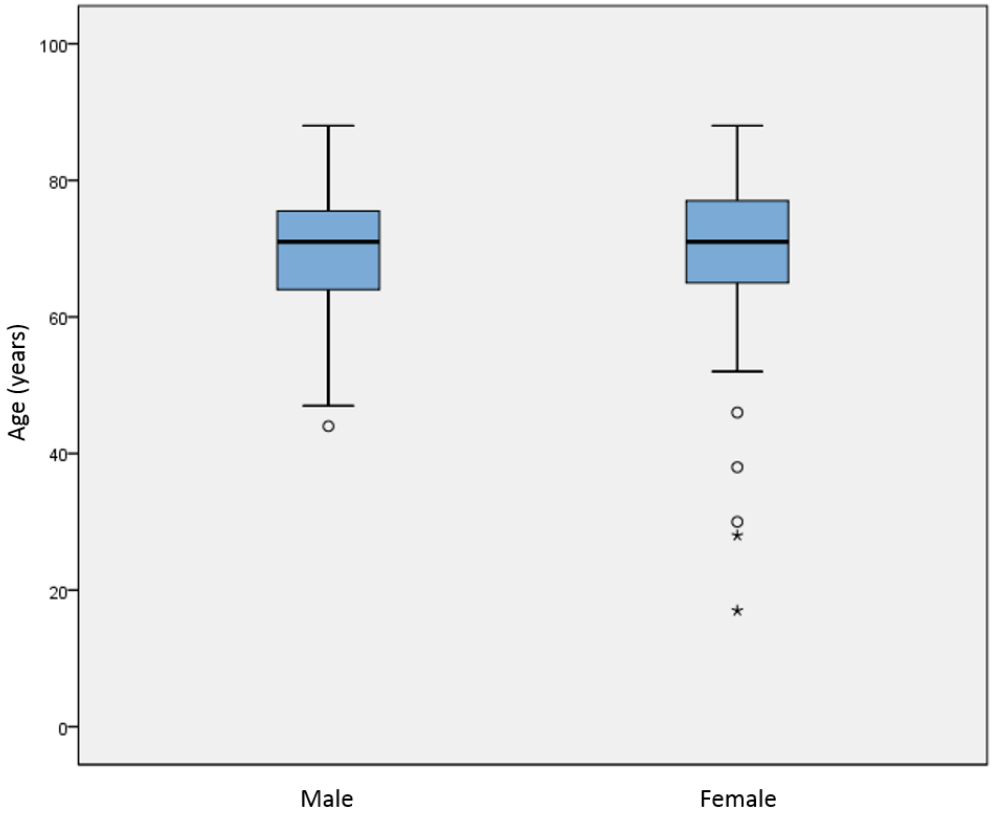


Figure 4: Boxplot of age distribution by gender. Circles denote outliers (an estimate point below the inner fence – Quartile(Q)1-1.5IQR or Q3+1.5IQR); "asterisks" refers to extreme outliers (an estimate point below the outer fence – Q1-3IQR or Q3+3IQR).

CKD aetiology

HT and type II Diabetes *Mellitus* (DMII) were the most prevalent aetiologies. HT alone or in association with other diseases was found to be the CKD aetiology in 67patients (50.4%); DMII alone or in association with other diseases was considered as CKD aetiology in 41 (30.8%) patients; in 18 patients (13.5%) CKD was considered as idiopathic. Figure 5 summarizes CKD aetiologies and its prevalence in the study sample.

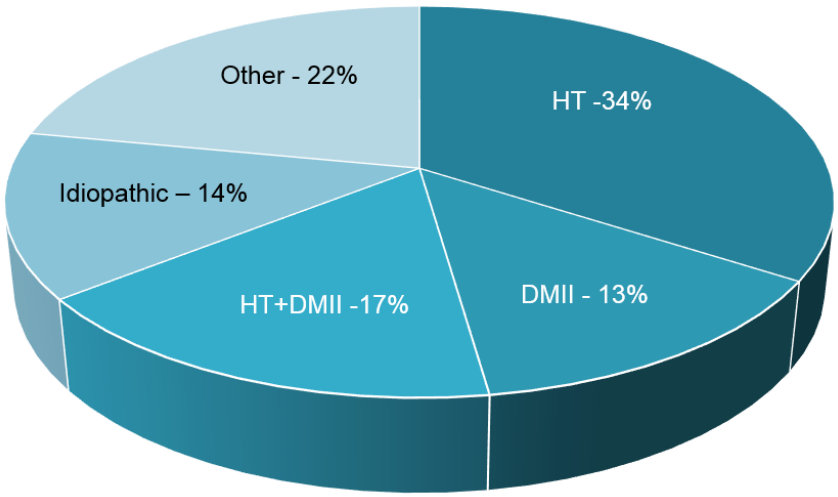


Figure 5: CKD aetiology pie chart.

The CKD aetiology as a group with 5 categories (HT, DMII, DMII+HT, Idiopathic, others) was independent of gender (Pearson's qui-square statistics of 3.688, with four degrees of freedom (df), two sided p-value=0.453). It was, however, dependent of age (Kruskal-Wallis two-sided p-value < 0.005; Levenne statistics=2.163 with df1=4 and df2=127, two sided p-value=0.077 with no rejection of the null-hypothesis of equal variances assumed; Sidak post-hoc analysis showed that the age of patients with "other" CKD aetiologies (median=65.0 years, IQR=19.0 years) was inferior to HT plus DMII patients' age (median=71.5 years, IQR=9.0 years; p=0.05) and "HT alone" patients' age (median=73.0 years, IQR=10.0 years; p=0.003).

Creatinine clearance / CKD stage

48 patients were under chronic HD program when they were referred for AVF construction.

Of the remaining 84 patients, 3 were in CKD stage 3, 46 patients were on stage 4 and 35 were on stage 5 (figure 6a).

Creatinine clearance of non-HD patients varied between a minimum of 8.86 ml/min to 32.10ml/min, with a median of 15.87 ml/min and an IQR of 7.82 ml/min (figure 6b and 6c).

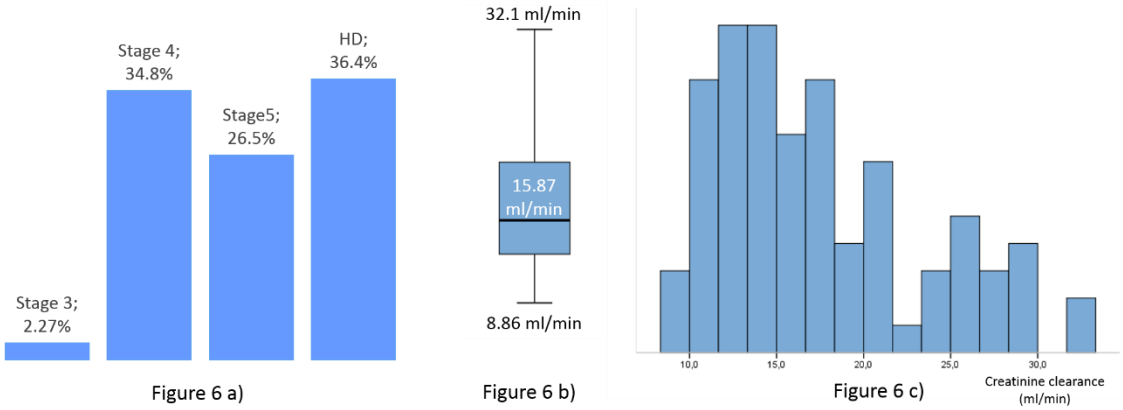


Figure 6: a) Bar chart: CKD stage distribution; b) boxplot creatinine clearance distribution; c) creatinine clearance histogram.

Comorbidities, smoking status and anti-platelet/anti-coagulant therapy

HT and DMII were the most prevalent comorbidities with 93.2% and 47.0%, respectively. Frequencies of comorbidities in the studied sample are detailed in table 2.

Table 2: Summary of descriptive statistics – comorbidities, smoking status and anti-platelet/anti-coagulant therapy.

Comorbidities variables	
HT, n (%)	123 (93.2)
Controlled, n (%)	58 (43.9)
Time in years, median (IQR)	15 (13)
DMII, n (%)	62 (47.0)
Insulin therapy, n (%)	32 (24.2)
Time in years, median (IQR)	5 (20)
HF, n (%)	39 (29.5)
NYHA I	9 (6.8)
NYHA II	20 (15.2)
NYHA III	10 (7.6)
NYHA IV	0 (0)
BMI (kg/m^2) mean (sd)	27.59 (5.08)
COPD, n (%)	18 (13.6)
Smokers, n (%)	23 (17.4)
Previous Smokers, n (%)	21 (15.9)
PAD, n (%)	108 (81.8)
Fontaine Classification II A, n (%)	5 (3.8)
II B, n (%)	13 (9.8)
III, n (%)	2 (1.5)
IV, n (%)	4 (3.0)
Anti-platelet therapy n, %	45 (34.1)
Anti-coagulant therapy n, %	20 (15.2)

HT – arterial hypertension; DMII – Type II Diabetes Mellitus; HF – Heart Failure; NYHA – New York Heart Association; BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; PAD – Peripheral Arterial Disease.

Vascular Access Surgery

63 left brachiocephalic fistula (LBC), 27 right brachiocephalic fistula (RBC), 27 left brachiobasilic fistula (LBB) and 15 right brachiobasilic fistula (RBB) were performed.

Termino-lateral anastomosis was more frequent in BC AVF and latero-lateral anastomosis was preferred in BB AVF (qui-square statistics=31.40, one degree of freedom, $p<0.001$). There were 7 patients with (5.3%) of haematomas. There were no surgical site infections.

27 patients had previous access in the contra lateral upper limb (three patients with two previous vascular access and one patient with three).

83 patients had no venous catheter on the jugular or brachiocephalic veins, 45 patients had a long-term HD catheter in the contra-lateral side of the AVF planned to construct and 4 patients had a long-term HD catheter in the ipsi-lateral side of the AVF planned to construct.

Pre-operative Colour Doppler Ultrasound

Table 3 describes pre-operative CDUS-derived parameters.

Table 3: Pre-operative CDUS vascular mapping and intra-operative hemodynamic parameters: summary of descriptive statistics.

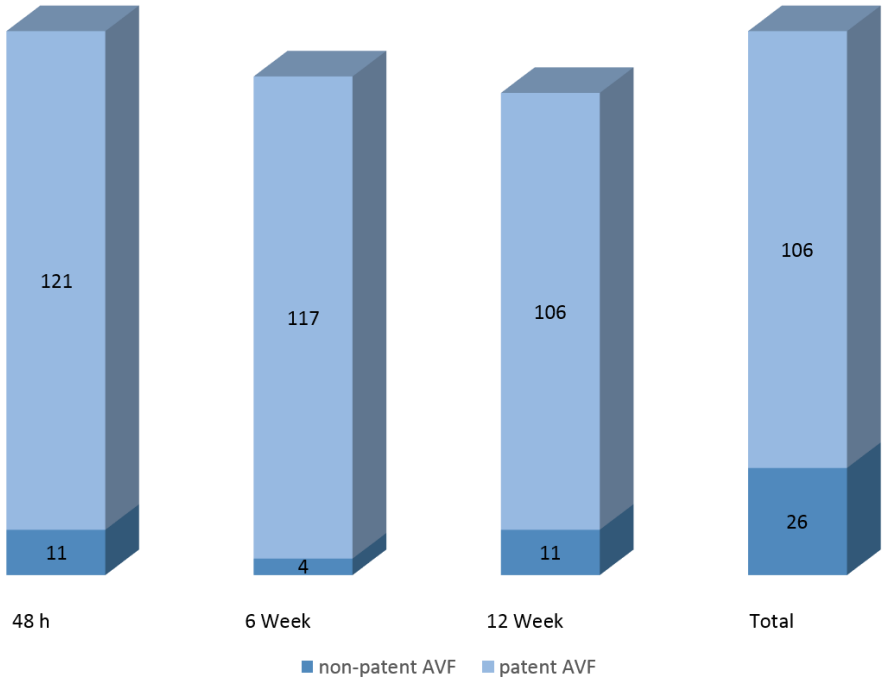
	Median	IQR		Median	IQR
VDT (mm)	4,30	1,58	**BAD (mm)**	4,30	0,9
VDWT (mm)	2,90	1,30	**Date_diff (days)**	27,50	62,0
VD_diff (mm)	1,20	1,10	**SBP (mmHg)**	164,0	44
VD_ratio	1,42	0,46	**DBP (mmHg)**	79	20
AV_dist (mm)	22,0	15,0	**PP (mmHg)**	89,0	33,75
BAF (l/min)	0,12	0,08	**MBP (mmHg)**	106,2	25,9

IQR – InterQuartile Range; VDT – Vein Diameter with Tourniquet; VDWT – Vein Diameter Without Tourniquet; VD_diff = VDWT-VDT; VD_ratio = VDWT/VDT; AV_dist – Distance between brachial artery and cephalic/basilica vein; BAF – Brachial Artery Flow; BAD – Brachial Artery Diameter; Date_diff = days between Pre-operative CDUS and VA surgery; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; PP – Pulse Pressure; MBP – Mean Blood Pressure

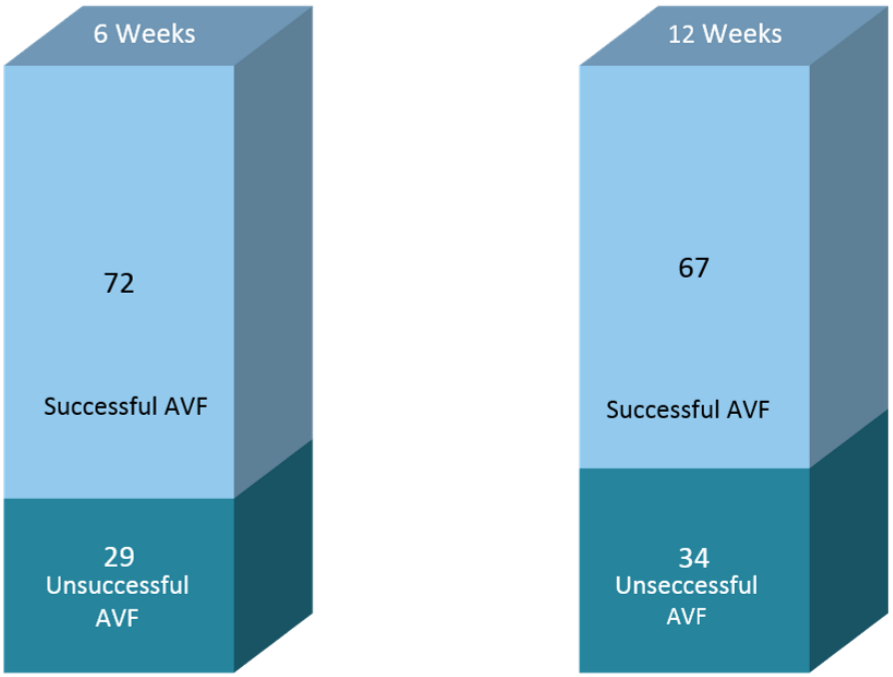
Outcomes

As previously mentioned in the methods section, AVF outcomes were measured as patent and non-patent and as AVF success or not success.

Of the 132 eligible patients with arm AVF surgery, 26 had non-patent AVF at 12 weeks of follow-up: 11 were non-patent at 48h, an additional 4 were non-patent at 6 weeks; and another 11 patients had non-patent AVF at 12 weeks (Figure 7a). Considering AVF success as a patent AVF with at least 600ml/min in brachial artery and a arterialized vein of at least 6mm in diameter [3-6, 71], at 6 weeks 29 (28.7%) were not successful AVF and at 12 weeks 34 (33.7%) patients had unsuccessful AVF (Figure 7b).



a)



b)

Figure 7 a) Bar chart: AVF patency at 48h, 6 week and 12 week follow-up; **b)** Bar chart: AVF success at 6 week and 12 week follow-up.

Outcomes summary:

- 48 hours primary patency was 91.7%.
- Six weeks primary patency was 88.6 %.
- Twelve weeks primary patency was 80.3%

- 71.3% AVF success at six weeks.
- 66.3% AVF success at twelve weeks.

Follow-up CDUS assessment

Table 4 summarizes the descriptive statistics of CDUS derived parameters at 6 weeks and 12 weeks follow-up.

Table 4: Summary of follow-up CDUS derived parameters (for patent AVF only).

	6 Weeks (n= 87)		12 Weeks (n=76)	
	median	IQR	median	IQR
Flow (l/min)	1.39	1.09	1.43	0.92
VD (mm)	7.4	2.70	8.40	3.00
PSV (cm/s)	185.2	89.7	192.40	110.80
RI	0,.8	0.14	0.46	0.15

Flow – Brachial Artery Flow; VD – Vein Diameter; PSV – Picosystolic velocity; RI – Resistance Index.

Five patients had a successful AVF at 6 weeks that became unsuccessful at 12 weeks (negative follow-up). On the contrary, four patients had a successful AVF at 12 weeks whereas they were unsuccessful at 6 weeks (positive follow-up) (figure 8). 70 patients had no changes in AVF success status.

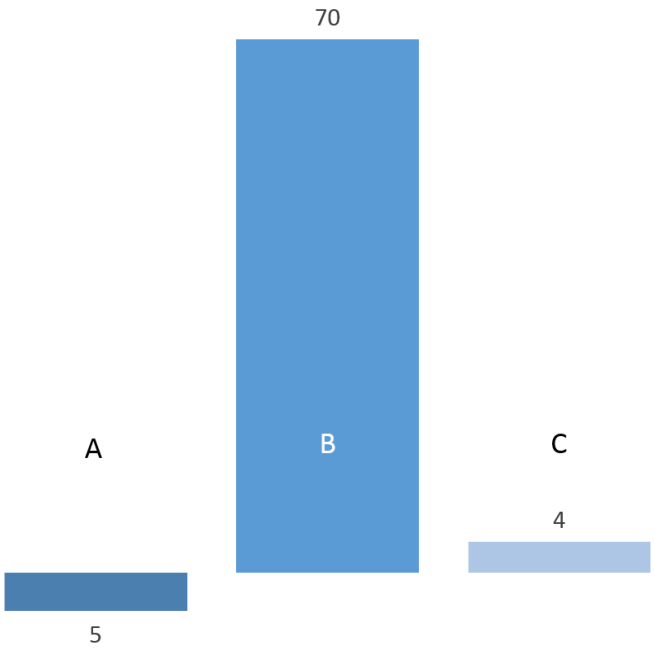


Figure 8: Absolut frequencies of patients with a negative follow-up (A), patients with no changes in AVF status (B) and patients with a positive follow-up (C).

Inferential statistics: univariate and bivariate analysis

Tables 5 and 6 summarize the univariate analysis according to study groups: patency vs non-patency at 48h, 6 weeks and 12 weeks (table 5) and AVF success vs AVF unsuccess at 6 weeks and 12 weeks follow-up (table 6).

Table 5: Summary of univariate analysis - Demographics, CKD aetiology and stage, comorbidities and AVF surgery data. Outcomes: patency at 48h, 6 weeks and 12 weeks follow-up.

	48h			**6 weeks**			**12 weeks**		
	Patent n=121	non patent n=11	p	Patent n=117	Non patent n=15	p	Patent n=106	non patent n=26	p
Age, median (IQR)	71.00 (15)	72.50 (8)	0.537	71.0 (15)	72.0 (19)	0.875	71.0 (15)	71.5 (10)	0.916
Gender | Male, n (%)	84 (69.4)	7 (63.6%)	0.955	82 (70.1)	9 (60.0)	0.427	76 (71.7)	15 (57.7)	0.167
CKD aetiology	-	-	0.828	-	-	0.664	-	-	0.730
CKD stage	-	-	0.823	-	-	0.785		-	0.371
Cr Cl, median (IQR)	15.90 (7.81)	15.30 (9.94)	0.994	15.90 (7.80)	15.30 (13.1)	0.942	16 (8.20)	14.2 (9.8)	0.387
Comorbidities									
HT, n (%)	113 (91.9)	10 (90.9)	0.755	109 (93.2)	14 (93.3)	1.00	99 (93.4)	24 (92.3)	1.00
Controlled HT, n (%)	53 (46.9)	5 (50.0)	0.851	51 (46.8)	7 (50.0)	0.821	48 (48.5)	10 (41.7)	0.548
dt_HT, median (IQR)	15.50 (13)	12.50 (14)	0.447	16 (13)	10 (14)	0.477	15.5 (13)	15 (14)	0.900
DMII, n (%)	56 (46.3)	6 (54.5)	0.599	55 (47.0)	7 (46.7)	0.980	49 (46.2)	13 (50.0)	0.730
Insulin therapy, n (%)	27 (50)	5 (83.3)	0.262	27 (50.9)	5 (71.4)	0.432	25 (53.2)	7 (53.8)	0.967
dt_DMII, median (IQR)	5 (20)	8.50 (19)	0.827	5 (20)	2 (18)	0.979	5.00 (20)	6.0 (19)	0.770
HF, n (%)	35 (28.9)	4 (36.4)	0.863	34 (29.1)	5 (33.3)	0.733	31 (29.2)	8 (30.8)	0.879
BMI, median (IQR)	27.56 (7.31)	28.31 (7.92)	0.296	27.57 (7.15)	27.57 (9.68)	0.880	27.84 (7.3)	27.57 (8.04)	0.866
COPD, n (%)	16 (13.2)	2 (18.2)	0.646	16 (13.7)	2 (13.3)	1.00	12 (11.3)	6 (23.1)	0.123

Table 5 (continued)	48h	6 weeks	12 weeks	48h	6 weeks	12 weeks	48h	6 weeks	12 weeks
	Patent n=121	non patent n=11	p	Patent n=117	Non patent n=15	p	Patent n=106	non patent n=26	p
Smoke Status			0.270			0.603			0.964
Never-smokers, n (%)	82 (67.8)	6 (54.5)		79 (67.5)	9 (60)		71 (67)	17 (12.9)	
Smokers, n (%)	19 (15.7)	4 (36.4)		19 (16.2)	4 (26.7)		18 (17)	5 (3.8)	
Previous-smokers, n (%)	20 (16.5)	1 (9.1)		19 (16.2)	2 (13.1)		17 (16)	4 (3)	
PAD, n (%)	23 (19)	1 (9.1)	0.688	21 (17.9)	3 (20)	0.736	19 (17.9)	5 (19.2)	1.000
Anti-platelet, n (%)	42 (34.7)	3 (27.3)	0.868	40 (34.2)	5 (33.3)	0.948	36 (34.0)	9 (34.6)	0.950
Anti-coagulant, n (%)	19 (15.7	1 (9.1)	0.884	19 (16.2)	1 (6.7)	0.467	18 (17.0)	2 (7.7)	0.362
AVF surgery									
BC AVF, n (%)	82 (67.8)	9 (81.8)	0.501	78 (66.7)	13 (86.7)	0.145	69 (65.1)	22 (84.6)	0.054
BB AVF, n (%)	39 (32.2)	2 (18.2)		39 (33.3)	2 (13.3)		37 (34.9)	4 (15.4)	
LL anast, n (%)	39 (32.2)	2 (18.2)	0.727	39 (33.3)	2 (13.3)	0.555	37 (34.2)	4 (15.4)	0.333
LT anast, n (%)	82 (67.8)	9 (81.8)		78 (66.7)	13 (86.7)		69 (65.1)	22 (84.6)	
Previous AVF									
0, n (%)	97 (80.2)	8 (72.2)		94 (80.3)	11 (73.3)		85 (80.2)	20 (76.9)	
1, n (%)	21 (17.4)	2 (18.2)	0.454	21 (17.9)	2 (13.3)	0.024	19 (17.9)	4 (15.4)	0.209
2, n (%)	2 (1.7)	1 (9.1)		1 (0.9)	2 (13.3)		1 (0.9)	2 (7.7)	
Counter lateral, n (%)	42 (34.7)	3 (27.3)	0.445	39 (33.3)	6 (40)	0.561	34 (32.1)	11 (42.3)	0.568
Surgical Complications n (%)	6 (5.0)	1 (9.1)	0.464	6 (5.1)	1 (6.7)	0.579	5 (4.7)	2 (7.7)	0.624

IQR – InterQuartile Range; CKD – Chronic Kidney Disease; Cr Cl – Creatinine Clearance; HT – arterial Hypertension; DMII – Type II Diabetes *Mellitus*; HF – Heart Failure; BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; PAD – Peripheral Arterial Disease; BC – BrachioChephalic; AVF – Arterio-Venous Fistula; BB – Brachiobasilic; LL – Latero-Lateral; anast – anastomosis.

Table 6: Summary of univariate analysis - Demographics, CKD aetiology and stage and comorbidities. Outcomes: VA success at 6 weeks and 12 weeks.

	AVF success 6 weeks			**AVF success 12 weeks**		
	Success (n=72)	Unsuccess (n=29)	p	Success (n=67)	Unsuccess (n=34)	p
Age, median (IQR)	72.0 (16)	73.0 (14)		73.50 (13)	68.0 (13)	
Gender | Male, n (%)	52 (72.2)	16 (55.2)	0.098	46 (68.7)	19 (55.9)	0.205
CKD aetiology	-	-	0.999	-	-	0.825
CKD stage	-	-	0.661	-	.	0.830
Cr Cl, median (IQR)						
Comorbidities						
HT, n (%)	66 (91.7)	28 (96.6)	0.670	63 (94.0)	32 (94.1)	1.00
DMII, n (%)	33 (45.8)	15 (51.7)	0.592	30 (44.8)	19 (55.9)	0.291
HF, n (%)	22 (30.6)	10 (34.5)	0.701	19 (28.4)	10 (29.4)	0.912
BMI	28.25 (7.90)	31.10 (6.67)		28.25 (7.90)	31.10 (6.67)	
COPD, n (%)	9 (12.5)	5 (17.2)	0.536	7 (10.4)	7 (20.6)	0.223
Smokers Status			0.842			0.645
Never-smokers, n (%)	49 (68.1)	18 (62.1)		44 (65.7)	25 (73.5)	
Smokers, n (%)	10 (13.9)	5 (17.2)		15 (22.4)	5 (14.7)	
Previous-smokers, n (%)	13 (18.1)	6 (20.7)		8 (11.9)	4 (11.8)	
PAD, n (%)	15 (20.8)	6 (20.7)	0.987	13 (17.6)	6 (19.4)	0.831
Anti-platelet, n (%)	25 (34.7)	11 (37.9)	0.761	22 (32.8)	13 (38.2)	0.590
Anti-coagulant, n (%)	13 (18.1)	2 (6.9)	0.220	11 (16.4)	3 (8.8)	0.373

Table 6 (continued)	AVF success 6 weeks			AVF success 12 weeks		
	Success (n=72)	Unsuccess (n=29)	p	Success (n=67)	Unsuccess (n=34)	p
AVF surgery						
BC AVF, n (%)	53 (73,6)	21 (72,4)	0,902	41 (61,2)	26 (76,5)	0,125
BB AVF, n (%)	19 (26,4)	8 (27,6)		26 (38,8)	8 (23,5)	
LL anast, n (%)	18 (25,4)	8 (27,6)	0,817	24 (36,4)	5 (14,7)	0,240
LT anast, n (%)	53 (74,6)	21 (72,4)		42 (63,6)	29 (85,3)	
Previous AVF						
0, n (%)	59 (81,9)	22 (75,9)	0,141	51 (76,1)	28 (82,4)	0,371
1, n (%)	12 (16,7)	5 (17,2)		14 (20,9)	4 (11,8)	
2, n (%)	0 (0,0)	2 (6,9)		1 (1,5)	2 (5,9)	
CV Catheter						
Counter lateral, n (%)	22 (30,6)	12 (41,4)	0,554	20 (29,9)	13 (38,2)	0,589
Ipsilateral, n (%)	2 (2,8)	1 (3,4)		1 (1,5)	1 (2,9)	
Surgical Complications n (%)	5 (6,9)	1 (3,4)	0,670	5 (7,5)	2 (5,9)	1,00

IQR – InterQuartile Range; CKD – Chronic Kidney Disease; Cr Cl – Creatinine Clearance; HT arterial Hypertension; DMII – Type II Diabetes *Mellitus*; HF – Heart Failure; BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; PAD – Peripheral Arterial Disease; BC – BrachioChephalic; AVF – Arterio-Venous Fistula; BB – Brachiobasilic; LL – Latero-Lateral; anast – anastomosis; CV – Central Venous.

Table 7 and table 8 summarize the univariate analysis of pre-operative CDUS-derived parameters according to study groups: patency vs non-patency at 48h, 6 weeks and 12 weeks (table 7) and AVF success vs AVF unsuccess at 6 weeks and 12 weeks follow-up (table 8).

Table 7: summary of univariate analysis – Pre-operative vascular mapping and intra-operative hemodynamic parameters. Outcomes: patency at 48h, 6 weeks and 12 weeks follow-up. Data presented as median (IQR).

	48h			**6 weeks**			**12 weeks**		
	Patent n=121	non patent n=11	p	Patent n=117	non patent n=15	p	Patent n=106	non patent n=26	p
VDT (mm)	4,5 (1,33)	3,7 (1,3)	0,259	4,5 (1,23)	3,6 (1,60)	**0,013***	4,5 (1,48)	3,6 (1,5)	**<0,001***
VDWT (mm)	2,9 (1,5)	2,6 (0,9)	0,769	2,9 (1,5)	2,5 (1,3)	0,081	2,95 (1,56)	2,5 (1,1)	**<0.001***
VD_diff (mm)	1,25 (0,92)	0,9 (1,6)	0,196	1,25 (0,92)	0,9 (1,6)	0,185	1,2 (0,9)	1,00 (1,40)	0,499
VD_ratio	1,49 (0,49)	1,36 (0,64)	0,344	1,49 (0,48)	1,38 (0,79)	0,754	1,457 (0,49)	1,50 (0,65)	0,190
AV_dist (mm)	23,5 (14)	22 (16)	0,650	22,5 (14)	28 (16)	0,296	23,5 (14)	22,0 (14,5)	0,436
BAF (l/min)	0,12 (17)	0,13 (15)	0,620	0,12 (0,08)	0,09 (0,09)	0,450	0,12 (0,08)	0,12 (0,07)	0,954
BAD (mm)	4,2 (0,925)	4,1 (1,00)	0,742	4,3 (0,9)	4,1 (1,2)	0,080	4,25 (0,875)	4,1 (1,15)	0,682
Date_diff (days)	27,0 (57)	40,0 (49)		26,5 (59)	56,0 (62)		26,5 (58)	46,0 (56)	
SBP (mmHg)	167 (37)	145 (23)	**0.013***	170 (39)	149 (22)	**0,011***	170 (41)	152 (31)	**0,004***
DBP (mmHg)	79,5 (17)	75 (15)	0.254	80,5 (18)	75 (13)	0,228	81 (18)	75 (15)	0,469
PP (mmHg)	90 (26,5)	64 (34)	**0,015***	90,5 (24,25)	77,0 (33,0)	**0,010***	92,5 (23)	77 (32,5)	**0,015***
MBP (mmHg)	107,5 (25)	102,3 (14,33)	0,075	108 (26,33)	102 (10,67)	0,066	108 (25,83)	102 (17,5)	0,164

VDT – Vein Diameter with Tourniquet; VDWT – Vein Diameter Without Tourniquet; VD_diff = VDWT-VDT; VD_ratio = VDWT/VDT; AV_dist – Distance between brachial artery and cephalic/basilica vein; BAF – Brachial Artery Flow; BAD – Brachial Artery Diameter; Date_diff = days between Pre-operative CDUS and VA surgery; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; PP – Pulse Pressure; MBP – Mean Blood Pressure. * Statistical Significance.

Table 8: summary of univariate analysis – Pre-operative vascular mapping and intra-operative hemodynamic parameters. Outcomes: VA success at 6 weeks and 12 weeks. Data presented as median (IQR).

	AVF success 6W			**AVF success 12W**		
	Success (n=72)	Unsuccess (n=29)	P	Success (n=67)	Unsuccess (n=34)	p
VDT (mm)	4,55 (1,55)	3,8 (1,25)	**0,004***	4,60 (1,50)	3,65 (1,38)	**0,000***
VDWT (mm)	2,9 (1,6)	2,6 (1,3)	0,10	2,90 (1,60)	2,50 (1,32)	**0,002***
VD_diff (mm)	1,25 (0,90)	1,00 (1,55)	**0,032***	1,20 (1,00)	1,05 (1,53)	0,098
VD_ratio	1,47 (0,44)	1,47 (0,75)	0,335	1,46 (0,50)	1,49 (0,69)	0,777
AV_dist (mm)	23,5 (14)	22,96 (14)	0,889	23,00 (14)	23,50 (14,50)	0,294
BAF (l/min)	0,10 (0,08)	0,12 ()	0,609	0,12 (0,08)	0,12 (0,065)	0,951
BAD (mm)	4,3 (0,875)	4,1 (1,15)	**0,030***	4,20 (0,90)	4,15 (1,25)	0,550
Date_diff (days)	21,00 (61)	42,00 (51)		26,00 (63)	41,00 (49,25)	
SBP (mmHg)	165,5 (42)	154 (31)	0,130	168,0 (42)	153,5 (34)	0,097
DBP (mmHg)	80,5 (20)	75 (15)	0,707	81 (17)	75 (17)	0,779
PP (mmHg)	90,5 (29,75)	83 (28,5)	0,068	94 (28,00)	82,5 (29,25)	**0,024***
MBP (mmHg)	106,83 (27,25)	102,67 (18)	0,390	108,00 (25,67)	102,16 (20,00)	0,328

VDT – Vein Diameter with Tourniquet; VDWT – Vein Diameter Without Tourniquet; VD_diff = VDWT-VDT; VD_ratio = VDWT/VDT; AV_dist – Distance between brachial artery and cephalic/basilica vein; BAF – Brachial Artery Flow; BAD – Brachial Artery Diameter; Date_diff = days between Pre-operative CDUS and VA surgery; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; PP – Pulse Pressure; MBP – Mean Blood Pressure. * Statistical Significance.

Brachial artery diameter was higher among males (median=4.40 | IQR=0.90 vs median=3.9 | IQR=1.05; Mann-Whitney mean rank 76.56 vs 44.17; sum of ranks = 6967 vs 1811; $p<0.001$) and significantly correlated with age (low positive

correlation ρ=0.198 p=0.023). All other pre-operative CDUS-derived parameters were independent of age and gender.

Table 9 summarizes the bivariate correlations between pre-operative vascular mapping CDUS-derived and intra-operative hemodynamic parameters.

Table 9: Bivariate non-parametric correlations between pre-operative CDUS-derived parameters and intra-operative hemodynamic parameters.

	VDT (mm)	VDWT (mm)	BAD (mm)	BAF (l/min)	VD_diff (mm)	VD_ratio	PP (mmHg)	MBP (mmHg)	SBP (mmHg)	DBP (mmHg)
VDT (mm)	-						0.063 p=0.473	0.115 p=0.190	0.045 p=0.612	-0.164 p=0.060*
VDWT (mm)	0.718 **p=0.000***	-					0.018 p=0.836	-0.100 p=0.256	-0.049 p=0.581	-0.135 p=0.127
BAD (mm)	0.079 p=0.369	0.105 p=0.233	-				0.171 p=0.051	0.100 p=0.254	0.139 p=0.111	0.058 p=0.506
BAF (l/min)	0.248 **p=0.004***	0.184 **p=0.037***	0.502 **p=0.000***	-			0.204 **p=0.019***	0.209 **p=0.016***	0.198 **p=0.023***	0.154 p=0.077
VD_diff (mm)	0.487 **p=0.000***	-0.177 **p=0.044***	-0.001 p=0.990	0.130 p=0.139	-		0.051 p=0.567	-0.065 p=0.465	-0.024 p=0.791	-0.094 p=0.290
VD_ratio	0.047 p=0.598	-0.605. **p=0.000***	-0.041 p=0.645	0.019 p=0.832	0.861 **p=0.000***	-	0.014 p=0.876	-0.008 p=0.925	-0.003 p=0.972	0.014 p=0.876
PP (mmHg)							-	0.645 **p=0.000***	-0.876 **p=0.000***	0.318 **p=0.000***
MBP (mmHg)								-	-0.921 **p=0.000***	0.911 **p=0.000***
SBP (mmHg)									-	0.702 **p=0.000***

VDT – Vein Diameter with Tourniquet; VDWT – Vein Diameter Without Tourniquet; VD_diff = VDWT-VDT; VD_ratio = VDWT/VDT; AV_dist – Distance between brachial artery and cephalic/basilica vein; BAF – Brachial Artery Flow; BAD – Brachial Artery Diameter; Date_diff = days between Pre-operative CDUS and VA surgery; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; PP – Pulse Pressure; MBP –

Regarding clinical relevant data, there was no correlation between VDT and VD ratio (Table 9, Figure 9a). There was a significant negative exponential correlation between VDWT and VD ratio (Table 9 and Figure 9b).

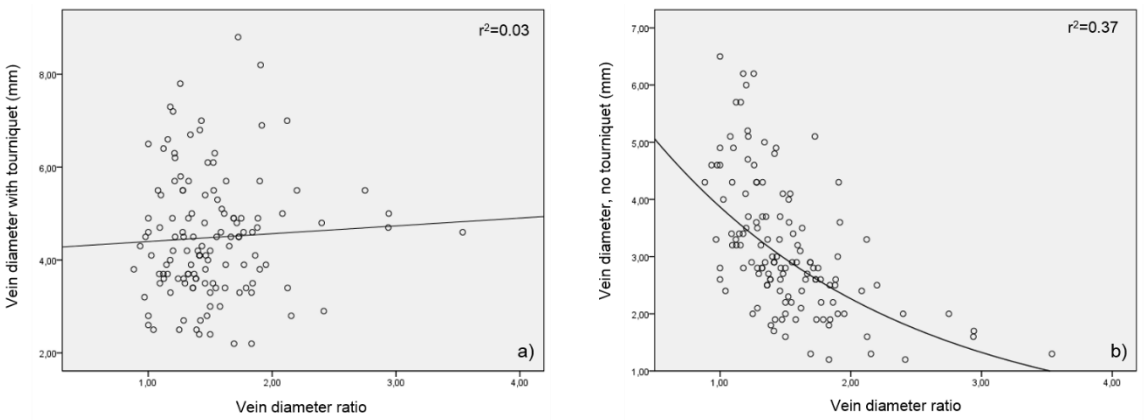


FIGURE 9: Correlation and best fit regression line between vein diameter with tourniquete and vein diameter ratio (a) and vein diameter without tourniquet and vein diameter ratio (b).

Vein diameter with tourniquete correlates better than vein diameter without tourniquet with vein diameter difference (Table 9, Figure 10a and 10b); coefficient=0.487 vs -0.177; r square=0.244 vs 0.036; p<0.002 vs p=0.044.

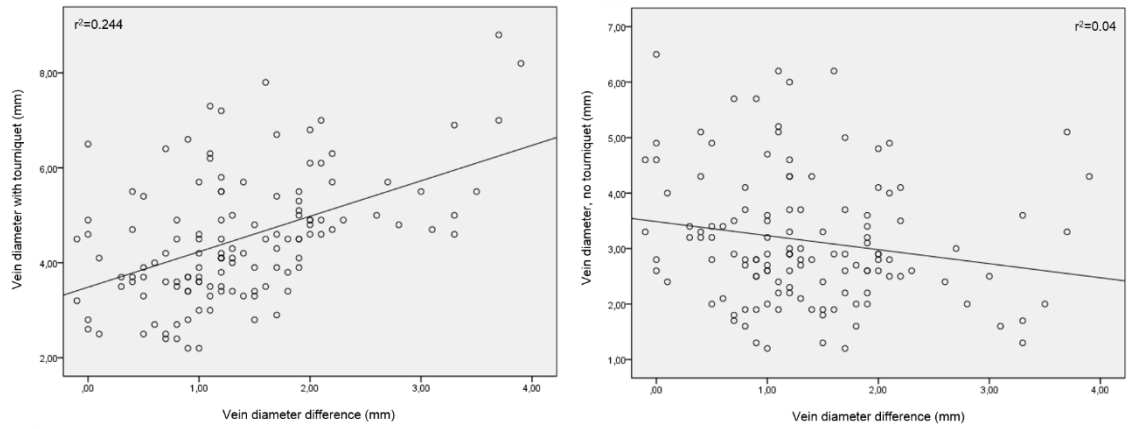


FIGURE 10: Correlation and best fit regression line between vein diameter with tourniquet and vein diameter difference (a) and vein diameter without tourniquet and vein diameter difference (b).

Although statistical significant the correlation between brachial artery diameter and brachial artery flow has a moderate coefficient of 0.50 and a low r2 (0.141) (Table 9 and Figure 11a).

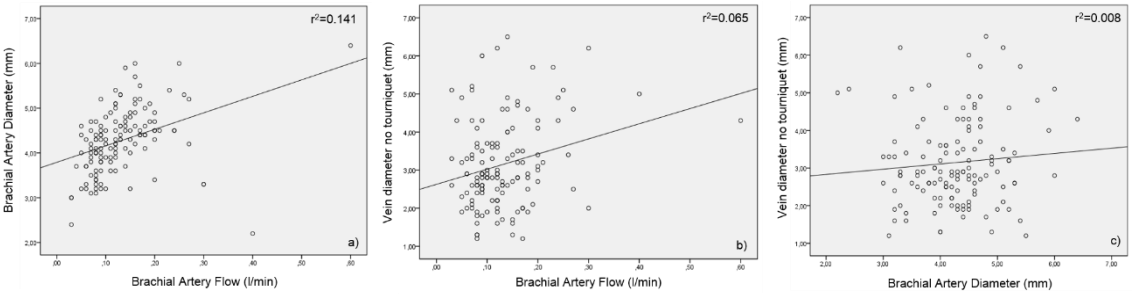


FIGURE 11: Correlation and best fit regression line between brachial artery diameter and brachial artery flow (a), vein diameter without tourniquet and brachial artery flow (b) and vein diameter without tourniquet and brachial artery flow (c).

Regarding vein diameter there was no significant correlation with brachial artery diameter and a poor correlation with brachial artery flow (Table 9 and Figure 11c). Comparing 6 weeks and 12 weeks follow-up CDUS-derived parameters (n=55), functional hemodynamic parameters (brachial artery flow, pico-systolic velocity and resistance index) were not statistically different. However, vein diameter was significantly higher at 12 weeks compared to 6 weeks (Table 10).

Table 10: Paired analysis between 6 weeks and 12 weeks CDUS-derived parameters.

	6W CDUS	12W CDUS	p (n=55)
BAF (l/min), median (IQR)	1.39 (1-09)	1.40 (0.85)	0.123
PSV (cm/s), median (IQR)	185.2 (89.7)	192.40 (110.8)	0.544
RI, median (IQR)	0.47 (0.11)	0.46 (0.15)	0.862
VD (mm), median (IQR)	7.40 (2.70)	8.40 (3.0)	**p<0.001***

6W CDUS – six weeks follow-up CDUS derived-parameters; 12W CDUS – six week follow-up CDUS derived-parameters; BAF – Brachial Artery Flow; PSV – Pico-Systolic Velocity; RI – Resistance Index; VD – Vein Diameter. * Wilcoxon non-parametric paired test; statistical significance.

Tables 11 to 12 summarize the bivariate correlations between 6 weeks follow-up CDUS-derived parameters (table 11) and 12 weeks follow-up CDUS-derived parameters (table 12).

Table 11: Bivariate non-parametric correlations between follow-up CDUS parameters at 6 weeks.

	BAF (l/min)	PSV (cm/s)	RI	VD (mm)
BAF (l/min)	-	0.659 **p<0.001***	-0.285 **p=0.009***	0.656 **p<0.001***
PSV (cm/s)	0.659 **p<0.001***	-	-0.114 p=0.300	0.583 **p<0.001***
RI	-0.285 **p=0.009***	-0.114 p=0.300	-	-0.254 **p=0.020***
VD (mm)	0.656 **p<0.001***	0.583 **p<0.001***	-0.254 **p=0.020***	-

BAF – Brachial Artery Flow; PSV – Pico-systolic velocity; RI – resistance index; VD – vein diameter. * statistical significance.

Table 12: Bivariate non-parametric correlations between follow-up CDUS parameters at 12 weeks.

	Qart (l/min)	PSV (cm/s)	RI	VD (mm)
Qart (l/min)	-	0,758 **p<0,001***	-0,195 0,096	0,662 **p<0,001***
PSV (cm/s)	0,758 **p<0,001***	-	-0,241 **0,039***	0,645 **p<0,001***
RI	-0,195 0,096	-0,241 **0,039***	-	-0,430 **p<0,001***
VD (mm)	0,662 **p<0,001***	0,645 **p<0,001***	-0,430 **p<0,001***	-

BAF – Brachial Artery Flow; PSV – Pico-systolic velocity; RI – resistance index; VD – vein diameter. * statistical significance.

At six weeks follow-up, there was a high positive correlation between brachial artery flow, pico-systolic velocity and vein diameter. There was a statistical significant negative moderate correlation with brachial artery flow and resistance index. There was no correlation with brachial artery flow and resistance index but there was a significant moderate negative correlation with vein diameter and resistance index (table 11).

At twelve weeks follow-up, there was a high positive correlation between brachial artery flow and vein diameter. There was a statistical significant negative moderate correlation with pico-systolic velocity and resistance index and between resistance index and vein diameter. There was no correlation with brachial artery flow and resistance index (table 12).

There was a significant positive correlation between six week and twelve week CUDS-derived parameters. The correlation was higher for brachial artery flow and pico-systolic velocity (Figure 12).

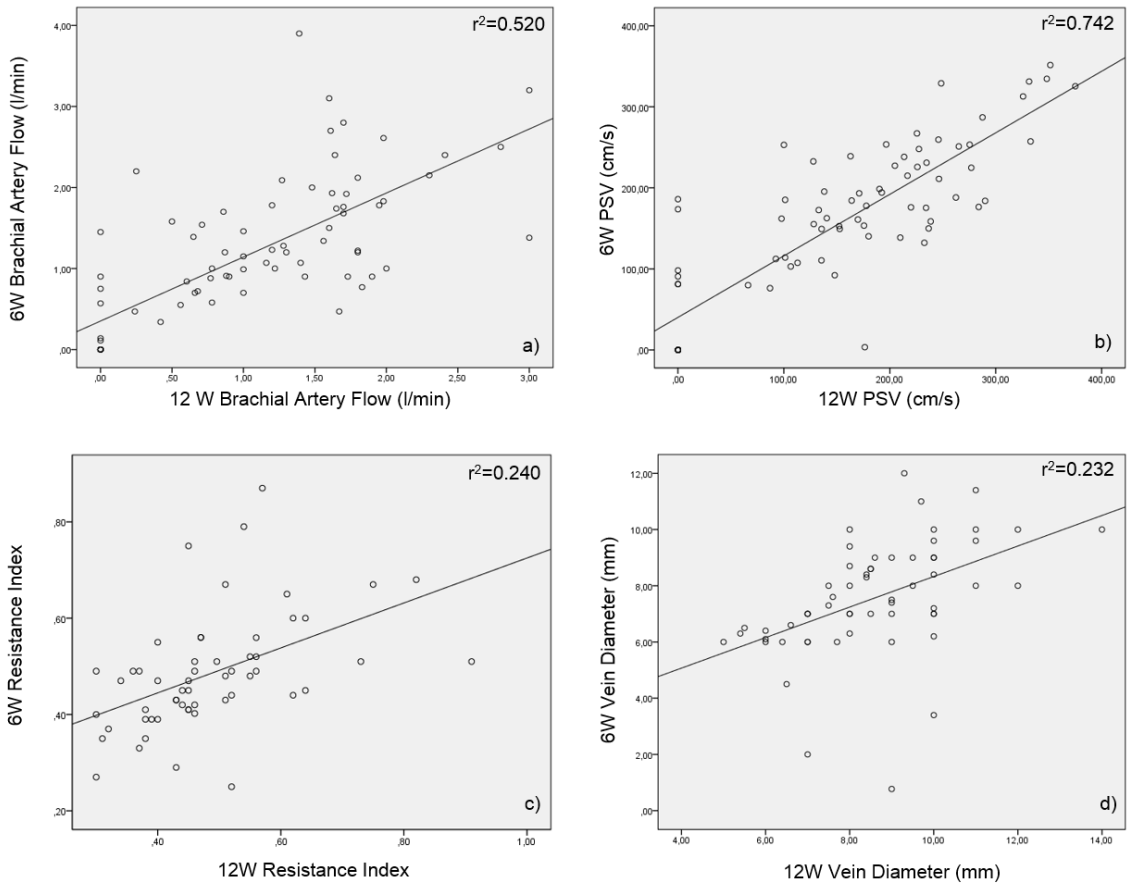


Figure 12: Bivariate non-parametric correlations between follow-up CDUS-derived parameters at 6 weeks and 12 weeks.

Inferential statistics: multivariate analysis

Multivariate analysis models were tested for demographics and HD status, comorbidities and CDUS-derived parameters with intra-operative hemodynamic parameters. A maximum of 4 independent variables were included in each model according to the sample size and power calculation. Univariate statistical significant variables and biological plausible variables were tested. Tables 13 to 15 present data from the best fitted multivariate model for each set of variables. Outcomes were patency at 48h and AVF success at 6 weeks and 12 weeks.

Table 13: Multivariate analysis of demographics and CKD disease

	OR [95CI]	p	Omnibus-x^2	Omnibus p
	48h			
Age	1.07 [0.96-1.19]	0.209		
Gender	0.39 [0.08-1.94]	0.252	3 163	0.367
Pre-HD/HD	1.02 [0.90-1.16]	0.741		
	6 week AVF Success			
Age	0.98 [0.92-1.05]	0.622		
Gender	1.94 [0.62-6.04]	0.253	1 936	0.586
Pre-HD/HD	1.01 [0.92-1.11]	0.835		
	6 week AVF Success			
Age	1.00 [0.94-1.06]	0.969		
Gender	2.45 [0.85-7.08]	0.097	2 844	0.416
Pre-HD/HD	0.98 [0.89-1.07]	0.614		

OR – Odds Ratio; 95CI – 95% Confidence Interval; HD – Heamodyalisis

Table 14: Multivariate analysis: comorbidities as independent variables.

	OR [95CI]	p	Omnibus-x^2	Omnibus p
	48h			
BMI	1.05 [0.92-1.22]	0.426	2 518	0.641
DMII	0.79 [0.17-3.71]	0.761		
CHF	0.68 [0.16-2.86]	0.603		
PAD	2.73 [0.32-23.7]	0.362		
	6 week AVF Success			
BMI	0.96 [0.87-1.06]	0.447	1.011	0.908
DMII	0.10 [0.34-2.99]	0.997		
CHF	1.14 [0.41-3.20]	0.800		
PAD	0.91 [0.29-2.81]	0.871		
	12 week AVF Success			
BMI	1.00 [0.91-1.10]	0.974	0.597	0.963
DMII	1.36 [0.508-3.64]	0.540		
CHF	1.11 [0.38-3.1]	0.849		
PAD	0.798 [0.253-2.51]	0.699		

BMI – Body Mass Index; DMII – type II Diabetes *Mellitus*; HF- Heart Failure; PAD – Peripheral Arterial Disease.

Table 15: Multivariate analysis: pre-operative CDUS-derived parameters as independent variables.

	OR [95CI]	P	Omnibus x^2 | p	Nagelkerke R^2	H-L p
	48h				
BAD	1.06 [0.43-2.59]	0.907	10 377 p<0.035	0.174	0.463
VDWT	0.74 [0.37–1.46]	0.385			
VD_ratio	0.21 [0.02-2.27]	0.197			
SBP	**0.98 [0.96-0.99]**	**0.019***			
	6 week AVF Success				
BAD	1.84 [0.91-3.72]	0.091	15 879 p<0.003	0.211	0.012
VDT	**1.80 [1.16-2.80]**	**0.009***			
VD_ratio	1.71 [0.53-5.53]	0.370			
SBP	1.01 [0.99-1.02]	0.280			
	12 week AVF Success				
BAD	0.69 [0.33-1.42]	0.317	23 944 p<0.001	0.297	0.449
VDT	**2.43 [1.46-4.03]**	**<0.001***			
VD_ratio	0.92 [0.27-3.11]	0.894			
PP	1.03 [0.99-1.05]	0.062			

OR – Odds Ratio; H-L – Hosmer and Lemeshow Test; BAD – Brachial Artery Diameter; VDWT – Vein Diameter without Tourniquet; VD_ratio – Vein Diameter Ratio; SBP – Systolic Blood Pressure; VDT – Vein Diameter with Tourniquet; PP – Pulse Pressure.

Regarding assumptions of logistic regression models, multicollinearity was not observed for these three regression models. For model fit and logit linearity pseudo (Nagelkerke) R^2 and Hosmer-Lemeshow tests were assessed.

Summary of inferential statistics: multivariate analysis

- Outcomes were independent of demographics, HD status (pre-HD vs HD) and comorbidities.
- Immediate pre-operative systolic blood pressure was a predictor of AVF patency at 48h.
- Vein diameter with tourniquet was an independent predictor of AVF success at 6 weeks and 12 weeks.

Receiver operating characteristics curves

Statistical significant independent predictors ROC curves were analysed.

The discrimination power of immediate pre-operative SBP for 48h patency and VDT for six weeks and twelve weeks AVF success were faire with areas under curve ≥ 0.7 (Figure 13 and Table 16).

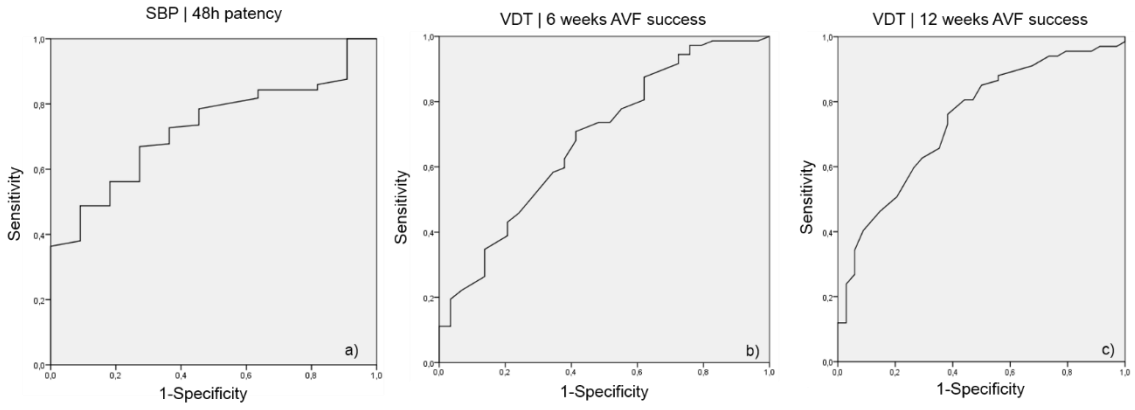


Figure 13: ROC curves for systolic blood pressure (SBP) and patency at 48h; vein diameter with tourniquet (VDT) and 6 weeks and 12 weeks AVF success.

TABLE 16: ROC Curve statistics

	AUC [95CI]	**p**	**AUC** [95CI]	**p**	**AUC** [95CI]	**p**
	48h		**6 Weeks**		**12 Weeks**	
SBP	0.73 [0.61-0.85]	0.013	-	-	-	-
VDT	-	-	0.69 [0.57-0.80]	0.004	0.74[0.64-0.84]	<0.001

AUC – Area Under Curve; [95IC] – 95% Confidence Interval; SBP – Systolic Blood Pressure; VDT – Vein Diameter with Tourniquet.

The optimized cut-offs for immediate pre-operative SBP was 154mmHg; for VDT at six weeks and twelve weeks AVF success was 3.9 mm. Each has a low to fair Youden Index ranging from 0.3 - for VDT at six weeks - and 0.4 - for SBP at 48h patency (Table 17).

TABLE 17: Youden Index for cut-off analysis

	Youden Index	**95CI_YI**	**Cut-off**	**95CI_cut-off**	**Sens**	**Specif**
SBP | 48h	0.40	[0.23-0.50]	154mmHg	[139-178]	72.7%	66.9%
VDT | 6W	0.29	[0.13-0.42]	3.9 (mm)	[2.9-5.5]	70.8%	58.6%
VDT | 12W	0.38	[0.14-0.50]	3.9 (mm)	[3.4-4.9]	76.1%	61.8%

SBP – Systolic Blood Pressure (mmHg); VDT – Vein Diameter with Tourniquet (mm); 95CI – 95% Confidence Interval; 6W – Six Week follow-up; 12W – Twelve Week follow-up; YI – Youden Index; Sens – Sensitivity; Specif – Specificity

Specificities and sensitivities associated to different cut-off values are described in tables 18 to 20 for immediate pre-operative systolic blood pressure, vein diameter with tourniquet for six weeks AVF success and vein diameter with tourniquet for twelve weeks AVF success respectively.

TABLE 18: Estimated specificity at fixed sensitivity and estimated sensitivity at fixed sensitivity for SBP|48h.

SBP (mmHg) | 48h AVF PATENCY			
		Estimated specificity at fixed sensitivity	
Sensitivity (%)	Specificity (%)	95CI	Cut-off
80,0	56,20	30,88 to 76,43	≤160,8
90,0	48,76	28,04 to 68,02	≤166,9
95,0	37,27	23,82 to 49,59	≤177,45
97,5	36,82	23,48 to 49,45	≤177,725
		Estimated sensitivity at fixed specificity	
Specificity (%)	Sensitivity (%)	95CI	Cut-Off
80,0	46,36	9,09 to 81,82	≤144,1
90,0	9,09	0,00 to 54,55	≤121,1
95,0	9,09	0,00 to 63,64	≤112,0
97,5	9,09	0,00 to 56,17	≤109,0

SBP – Systolic Blood Pressure, 95CI – 95% Confidence Interval

TABLE 19: Estimated specificity at fixed sensitivity and estimated sensitivity at fixed sensitivity for VDT | 6 Weeks AVF success.

VDT (mm) | 6 Week AVF Success			
		Estimated specificity at fixed sensitivity	
Sensitivity (%)	Specificity (%)	95CI	Cut-off
80,0	39,31	17,07 to 58,62	>3,52
90,0	31,72	14,49 to 51,72	>3,34
95,0	24,14	4,91 to 43,14	>2,98
97,5	20,00	0,47 to 42,24	>2,78
		Estimated sensitivity at fixed specificity	
Specificity (%)	Sensitivity (%)	95CI	Cut-off
80,0	38,47	14,70 to 56,67	>4,81
90,0	24,10	8,33 to 44,31	>5,46
95,0	20,69	6,94 to 39,81	>5,61
97,5	11,11	1,39 to 20,45	>6,43

VDT – Vein Diameter Tourniquet, 95CI – 95% Confidence Interval

TABLE 20: Estimated specificity at fixed sensitivity and estimated sensitivity at fixed sensitivity for VDT | 12 Weeks AVF success.

VDT (mm) | 12 Week AVF Success			
			Estimated specificity at fixed sensitivity
Sensitivity (%)	Specificity (%)	95CI	Cut-off
80,00	56,67	35,88 to 74,89	>3,81
90,00	36,47	7,73 to 60,00	>3,34
95,00	21,62	0,00 to 46,95	>2,94
97,50	1,99	0,00 to 27,50	>2,34
			Estimated sensitivity at fixed specificity
Specificity (%)	Sensitivity (%)	95CI	Cut-off
80.00	38,47	14,70 to 56,67	>4,81
90,0	24,10	8,33 to 44,31	>5,46
95,0	20,69	6,94 to 39,81	>5,61
97,5	11,11	1,39 to 20,45	>6,43

VDT – Vein Diameter Tourniquet, 95CI – 95% Confidence Interval

DISCUSSION

DISCUSSION

The aim of this study is focused on pre-operative predictive factors for a proximal functional AVF.

To answer this question, it should be kept in mind the **mechanisms that may lead to AVF failure**, all the challenges regarding **controlling** for bias and confounders, and the heterogeneity of the outcome definitions.

Mechanisms for AVF failure:

An unsuccessful AVF may be due to thrombosis (non-patent AVF) or to non-maturing AVF [44, 72-74].

Thrombosis/thrombogenesis has been explained many years ago by the classic Virchow triad: abnormal blood flow, abnormal vessel wall and abnormal blood constituents [44, 74-81]. All AVF patients had:

- a locally abnormal blood flow due to the AVF itself or due to hypotension periods associated to HD, dehydration (from a clinical point of view especially critical in summer), or other factors [43, 66-68, 73-74].
- a biological vessel wall response due to this locally abnormal blood flow [80, 82, 83];
- an uraemia environment which is associated to a hypercoagulability state.

In fact, uraemia has been associated with pro-inflammatory and pro-thrombotic molecular factors such as high-sensitivity C-reactive protein, D-dimers, soluble IL-2 receptor, IL-6, von Willebrand factor, p selectin, and thrombin/antithrombin

III. This cascade is enhanced by thromboxanes and factors released from the platelets themselves [83-88]. Therefore, all AVF patients are prone to AVF thrombosis. It is easy to understand the acute changes in local blood flow due to AVF surgery. However, the poor understanding of the pathobiology in the vein wall response to blood flow change remains a critical barrier [89]. Despite the heterogeneity of the factors associated with AVF patency, many of these factors seem to act through similar pathologically molecular mechanisms [90].

Intimal hyperplasia (IH) has been consistently implicated as a major mechanism of vein response to shear blood flow stress leading to non-matured AVF and thrombosis [12, 90-94].

The histology of intimal hyperplasia is characterized by an abundance of contractile smooth muscle cells, myofibroblasts, fibroblasts, and macrophages, which eventually narrow the venous outflow leading to stenosis and a reduction in blood flow or in many cases thrombosis [12, 91-94].

There are many studies that have demonstrated that intimal hyperplasia occurs through several vascular biology pathways, including inflammation, uraemia, hypoxia, shear-stress, and thrombosis. These mechanisms are thought to work in a synergistic way conducive to negative remodelling and leading to fistula failure [91-93, 95, 96].

Unlike atherosclerosis, which is a chronic, inflammatory, fibroproliferative disease of the vascular wall that gradually occurs in time, IH is a rapid adaptive response to injury of the endothelium by surgical, hemodynamic, immune or metabolic stresses [82, 97].

From a mechanistic point of view, the events leading to IH can be divided in:

- blood flow changes and endothelial damage phase
- inflammatory phase
- proliferation phase
- remodelling phase

AVF surgery leads to a local and systemic hemodynamic acute change. Different theories and hypothesis tried to explain blood flow changes: high shear stress [98-101], low–oscillatory shear stress [56, 102], turbulence, and temporal gradient of shear stress [103-105]. Acute blood flow changes leads to endothelial damage and myointimal endothelial activation, a pro-inflammatory milieu with gene transcription and protein expression, towards myointimal hyperplasia with deposition of fibroblasts, myofibroblasts and macrophages [82].

Although neointimal hyperplasia might be the leading reason for early (less than three months) AVF failure, other factors are thought to act through it or independently [41, 44, 72, 74, 106-109].

According to all the above, AVF early failure acts clinically and biologically as a multifactorial and polygenic disease.

Controlling for bias and confounders and heterogeneous outcomes definitions

There are no randomized clinical trials (RCT) which specifically address this study question. To randomize patients to different surgical procedures or to randomly select patients according to pre-operative CDUS derived parameters would lack clinical equipoise - there is no equivalent surgical procedure to brachiobasilic/brachiocephalic AVF with similar morbidity for a specific patient – making it unfeasible.

There are previous observational prospective studies which aim to associate demographics, comorbidities, CKD stage, pre-operative CDUS and hemodynamic parameters [8, 10, 12, 13, 23, 26, 27, 32, 34, 40, 42, 45, 46, 49, 71, 73, 82, 106, 107, 110-126]. These studies have conflicting results, mostly due to lack of proper control of bias and confounders and some of them also lack power. Only one prospective study was found aiming to stablish cut-offs for CDUS pre-operative parameters [37]. However, this study included only radiocephalic fistulas.

No observational prospective studies were found regarding cut-offs for pre-operative CUDS parameters for BC or BB AVF fistulas.

An additional major methodological issue is the lack of homogeneity of outcome definitions and evaluation:

- some studies define outcome as patent AVF [22, 112];
- others define outcome as mature AVF [127];
- others define outcome as a functional AVF [128];
- some studies evaluate AVF outcomes clinically which might be measured as continuous thrill and bruit [112] or successful needle cannulation for HD [129, 130] [22, 127, 128];
- some studies evaluate AVF outcomes by Doppler ultrasound [44, 131] [127] [37].[115];
- time of patency/mature/functional AVF assessment varies among studies between 24h, 48h, 6 weeks, 8 weeks and 12 weeks.

From a clinical point of view, a successful AVF surgery means a patient that can be cannulated for an efficient HD treatment with no complications. These would

exclude patients with end-stage CKD under conservative treatment. However, the standard-of-care supported by international guidelines [3-6] states that an AVF should be performed “when glomerular filtration rate is less than 15 mL/min/1.73 m^2 […] anticipating the start of HD from […] at least 2 to 4 weeks before the initial puncture” [4]. Moreover, there are other reasons for clinical unsuccessful AVFs that are not associated with local and/or systemic hemodynamic and cannot be predicted by pre-operative CDUS namely tortuous veins [106, 107, 117, 125].

Therefore, there are two different clinical settings: HD patients, evaluated clinically as a successful cannulation for efficient HD, and pre-HD patients, evaluated clinically and by CDUS. Ideally different designs should be performed to study these different settings. However, for most prospective observational single centre studies, these would compromise sample size and power analysis. Also, HD patients are subject to arterial pressure variations which have been associated with AVF failure [106].

In this study, CDUS parameters were use according to the “rule of six” (an AVF flow of at least 600ml/min and a vein diameter of 6mm or higher) to assess fistula success, assuming that the rule of six is associated with clinical success [3, 4, 6]. HD vs pre-HD patients were included and this was included as a binomial variable in multivariate regressive models.

As a multifactorial and polygenic condition, when studying AVF failure, there are numerous potential bias and confounders.

In accordance to the literature [8, 10, 12, 13, 23, 26, 27, 32, 34, 40, 42, 45, 46, 49, 71, 73, 82, 106, 107, 110-126] confounders were classified as demographics,

CKD related factors comorbidities, anatomic variants and AVF surgery and complications (Figure 1).

Restriction, proxy variables and multivariate analyses were the strategies used to adjust/control for confounders [132, 133]:

- **Demographics, CKD related factors and comorbidities**

Cardiovascular risk factors and comorbidities - including obesity, smoking and type II diabetes *mellitus* (DMII) - are potential confounders since they influence CDUS parameters and have been associated to AVF failure [106, 121, 123].

Proxy variables were used to assess severity of hypertension and type II Diabetes *mellitus* (controlled HT, insulin therapy and time of diagnosis); additional demographics, comorbidities and surgical AVF variables were tested in univariate and multivariate models.

Chronic hypoxia such as in Chronic Obstructive Pulmonary Disease (COPD) patients has been associated with vascular remodeling and neo-intimal hyperplasia. Studies have described lung vascular wall and carotid artery wall damage in COPD patients [134, 135]. There are no studies specifically addressing the risk of thrombosis in COPD patients. However, there is evidence of chronic hypoxia effects on gene expression and lung and systemic vascular wall [135], as there is evidence suggesting vascular remodeling as a risk factor for AVF thrombosis [12, 91, 92, 134, 135]. Therefore, COPD might act as a confounder.

Hypotension induced HD has long been recognized as a risk factor for AVF thrombosis [44, 106, 111, 121, 123, 136]. Pre-hemodialysis (Pre-HD) vs HD (HD) patients submitted to AVF surgery might induce selection bias.

Anti-platelet and anticoagulant drugs have been studied and data are conflicting regarding their impact on AVF success [109, 112, 114, 120, 124, 128, 137]. The same is true for patients with pace maker, central venous lines or dialysis catheters, although these might act as covariates of pre-HD vs HD patients. [74, 107, 108, 113].

Etiology of CKD is more likely to act as a covariate with age, gender and cardiovascular comorbidities than a confounder or bias. According to ERA-EDTA, NPS and US Renal Data System [2, 138, 139], HT and DMII are the most prevalent etiologies. They are more associated with older age and cardiovascular comorbidities than congenital CKD.

Anti-platelet and anticoagulant drugs have been studied and data are conflicting regarding their impact on AVF success [109, 112, 114, 120, 124, 128, 137]. The same is true for patients with pace maker, central venous lines or dialysis catheters, although these might act as covariates of pre-HD vs HD patients. [74, 107, 108, 113].

- **Anatomic variants and AVF surgery and complications**

Arterial anatomical variants such as high axillary/brachial artery bifurcation and patients with failure of ipsilateral previous access might have different hemodynamic patterns which in turn might influence the AVF success rate without a measurable difference in CDUS. This is a potential selection bias and therefore these were considered as exclusion criteria (restriction). Conflicting data and low quality evidence exist regarding the influence of high brachial artery bifurcation in AVF outcomes [42, 61] . Since it was not the aim of this work to study this feature as a predictive factor for AVF outcome, and given additional

power would be needed to include it in multivariate analysis, those patients were excluded to avoid potential bias.

There is no evidence regarding the influence of distal AVF thrombosis in proximal artery hemodynamics. There is a logical rational that blood flow, velocity, luminal diameter and compliance may change in a non-measurable way after distal AVF thrombosis and this might influence the outcome of proximal new AVF. The same is true for BB AVF construction after BC AVF failure (and vice-versa). Therefore, to avoid potential bias, patients with previous ipsilateral definitive vascular access were excluded.

Surgical skills might be different across surgeons and centers (and this is a recognized factor for AVF success [4]). Multicenter studies are usually a method to overcome this issue. Since this is a single center study, one has to keep in mind this potential limitation.

Surgical complications might influence AVF results since hematomas or infections are prone to thrombosis, even on very suitable veins and arteries. Anticoagulant therapy has been associated with hematomas and AVF thrombosis [109, 112, 114, 120, 124, 128, 137] even with suitable veins and arteries for an AVF surgery. Since they are measurable variables, these patients have not been excluded, and these variables have been considered in multivariate analysis.

The interactions between the previously mentioned variables are represented in the direct acyclic graph (DAG) in Figure 1.

Selection bias is a necessary flair since according to the standard-of-care, patients with low blood pressure and poor upper limb vascular bed may be referred for other procedures with better outcome. Patients with optimal distal

vascular bed should be referred for distal AVF. Selection bias in this study needs to be adequately interpreted: the results of this study are representative of patients that are not indicated for distal AVF and are indicated for a proximal AVF surgery.

Patency and AVF Success Rate

Primary patency rates and AVF success rates are similar to previous studies where early primary patency of BC and BB AVF ranges between 63% and 90% [8-10, 128].

This spectrum of results across different studies regarding primary patency is probably due to different study and outcome definitions and assessment protocols as previously discussed.

Demographic, CKD Disease and Comorbidities

Primary patency and AVF success in this study were independent of demographics, CKD stage and aetiology, presence of central venous line and comorbidities (univariate and multivariate analysis). The influence of comorbidities in AVF success is heterogeneous across studies. A study conducted by *Murphy et.al (2002)* [140] with n=293, exemplifies the former by finding no association between diabetes mellitus and failure of elbow AVF. Other authors demonstrated identical patency among diabetic and non-diabetic patients [141]. Covariates of systemic arterial disease (coronary artery disease, cerebrovascular disease, smoking, PAD) are frequently associated with AVF failure [10, 13, 15, 32, 59, 72, 117, 123, 125, 141, 142]. There is an empirical and biological rationale to explain these associations. Systemic arterial disease with

calcification, arterial stiffness and endothelial activation leads to low pressure and low flow in the AVF arterial inflow - which was an independent predictor of AVF patency at 48h - as well as to an inflammatory and pro-thrombotic milieu which has been claimed as the most important physiopathological factor for AVF maturation and thrombosis [12, 46, 91, 93, 95].

According to the literature, female gender - probably due to factors related to lower vascular capacitance and reduced ability to reach the peak systolic flow with the fist clenching maneuver [7, 72, 119] – type II diabetes mellitus [13, 33, 46, 123, 140-142], smoking [109, 134, 141] and severe obesity (BMI> 35kg/m^2) [13, 48] have been associated with a greater risk of AVF failure. Nonetheless, most studies either do not analyze distal and proximal AVF separately, or only analyze distal AVF [8, 72, 109, 119, 141]. In this study, no statistical associations were found between the former variables and the AVF patency and success. These results may suggest a less prominent influence of these factors on proximal AVF comparatively to the distal one, or lack of power to detect a small effect difference.

Advanced age is assumed to be a risk factor for AVF failure. However, most studies are not consistent in the definition of advanced age and include proximal as well as distal AVF, the later having a greater likelihood of being unsuccessful in an elderly population [72, 119]. Additionally, it should also be taken into account that, in many studies, only comorbidities and not anatomical factors, such as arterial and venous diameter, are evaluated. In this study, similarly to other authors [72], no association was found between age and failure. These findings suggest that age related effects may be of less relevance in proximal vessels

compared to distal ones so that a proximal AVF may be safer in elderly patients [72]. However, no comparative analysis was conducted in the present study.

Presence of a temporary catheter or a long-term catheter for vascular access is thought to be a risk factor for AVF surgery due to venous drainage obstruction, pro-thrombotic, inflammatory and infectious milieu or association (confounding) with blood pressure liability and post-dialytic hypotension [44, 106, 111, 136]. In this study there were no associations between central venous catheters in subclavian or jugular veins for intravenous therapy and/or hemodialysis.

Although patients with AVF failure at 48h presented a higher prevalence of COPD it was not statistically significant. COPD association with AVF patency could be explained due to endothelial dysfunction stemming from chronic hypoxemia [90, 134, 135, 143]. COPD association to AVF patency is less studied than age, gender, DMII and cardiovascular disease. Further assumptions regarding COPD association need further studies, specifically designed to answer this question. In our sample, only two of 11 48h-non-patency had a COPD diagnosis.

No associations with failure were found regarding cardiovascular and metabolic diseases (CHF, PAD, BMI, DM II, anti-platelet or anticoagulant agents).

As previously stated, association of comorbidities with AVF patency and success are inconsistently and heterogeneously reported [8, 72, 109, 119, 120, 131, 141]. A possible explanation is that, even with major vascular systemic disease, the local hemodynamic in upper arm ranges between values that do not compromise AVF patency and maturation, which might be different for the distal forearm with lower arterial flow and a lower arterial and vein diameter, where comorbidities are consistently associated with AVF failure [10, 116, 123, 142].

Regarding antiplatelet and anticoagulant agents, *Yevzlin et al.* based on the USRDS (*United States Renal Data System*), demonstrated that the use of acetylsalicylate (ACS), dipyridamole or ticlopidine increased the risk of distal and proximal AVF failure (*N=257*) [144]. *Hasegawa, T et al.*, using the Dialysis Outcomes and Practice Patterns Study (DOPPS) data (n=612 taking ACS e n=2203 not taking ACS), found a 37% relative risk reduction for AVF failure with 1-year *(p=0.03)* of consisting therapeutically adhesion [114]. Dember, L *et al.* in an RCT compared placebo (n=431) and clopidogrel (n=435) initiated in the first day post AVF creation (loading dose of 300mg and maintenance dose of 75mg/day). At 6-weeks post-surgery the thrombose rates were 12.2% for the clopidogrel group and 19,5% for the placebo (RR=0,63; IC 95% 0.46-0.97, *p=0.018*). No significant differences were found in the hemodialysis usability rate at 1-year, or in the incidence of side effects among groups [112]. A 2008 Cochrane meta-analysis by *Osborn et al*. [137] demonstrated a significant benefit in AVF and graft patency with the use of anti-platelet drugs when compared to placebo. A 2015 update, which included 6 more RCTs, concluded that ticlopidine had a beneficial effect on AVF patency at 1month post-creation and that, due to the methodological characteristics and heterogeneity of the available literature, there was not sufficient evidence to support the benefit of other anti-platelet agents [124]. Acetylsalicylic acid is also an anti-inflammatory agent, which may contribute to reduce neo-intima juxta-anastomotic hyperplasia, and therefore reduce the risk of venous stenosis and access failure. Both these effects may be detrimental on an initial phase in which the surgical trauma causes the endothelium to release prothrombotic factors [114, 120]. These protective effects may be lost or reduce with time due to the stabilization and repair of structures

and respective tissues. In the present study, no associations were found with both antiplatelet and anticoagulant agents.

As a conclusion, in our sample, unmeasured factors other than age, gender, CKD stage and comorbidities led to AVF thrombosis and non-maturation.

Pre-operative CDUS-derived parameters

Most studies evaluating **arterial diameter** refer to the radial artery for which the minimal acceptable diameter for AVF creation seems to be 1,5-1,6mm – considering the patient's characteristics a proximal AVF may be recommended in *borderline* cases [23, 116, 141]. In a prospective study *Mohamed, A et al.* significantly associated AVF failure at 3 months with brachial artery diameter. The diameters were 2,3mm in the failure group (n=6) and 2.8mm in the patency group (n=81), (*p=0.001*) [145]. In the present study, arterial diameter did not influence AVF outcome at 48h or at 3 months.

Kordzadeh et al. suggest that there is a minimal diameter value above which this parameter probably does not influence patency. The ideal radial arterial diameter proposed is 2.4mm, not considering patient's characteristics [116]. In the present study, the small spectrum of brachial artery diameter, with a minimal of 3mm recorded, may explain why no association was found since this diameter could be higher than the minimal diameter suitable for a functional AVF. This represents a selection bias that cannot be avoided since patients with severe arterial disease should not be referred for upper arm ipsilateral proximal AVF. A radial artery diameter > 1,5mm has been associated with a greater AVF flow at 12-weeks post-surgery: 347.9ml/min vs 521ml/min, *p=0.03* [146]. This is explained by the

inversely proportional relationship between **blood flow** resistance and vessel's r^4: with an increase in diameter there will be a proportional increase in flow [23, 34, 146]. As expected, a positive correlation between pre-operatively measured arterial diameter and flow was obtained. Diameter and flow measurements were taken during a single session, in different conditions (of temperature, stress, time to surgery, therapeutics, etc.) among patients, without monitoring of parameters such as heart rate or blood pressure, which may affect the homogeneity of the results and condition the predictive capacity of the model. Intra-operative AVF flow has been reported as a predictor of success and 1-year primary and secondary patency of RCAVF if > 200 ml/min[147]. Regarding proximal AVF, previous studies describe an association between the mean intra-operative proximal AVF flow (measured at 5 minutes) of 260ml/min and failure in the first 3 months *(p= 0.004),* n=6 [116, 145]. In the present study only pre-operatively measured arterial blood flow was addressed and it was not an independent predictor of AVF patency or AVF success. This value, measured pre-operatively, may not reflect the one that shall be obtained once the AVF is created. Also, the pre-operative measure does not predict the vessel spasm caused by the intervention, which reduces flow. The AVF inflow is dependent of a continuous pulse pressure and blood flow. However, it is very difficult to design a methodology to have a non-invasive continuous assessment of arterial blood flow for at least 48h. A retrospective study demonstrated an association between post-operative SBP (at 30 minutes) and distal and proximal AVF patency at 12 months [109]. SBP values of 120-139mmHg conditioned a thrombose rate 68% inferior compared to the group with a SBP <119mmHg [109]. In the present study, intra-operative SBP (measured as stated in methods) was an independent predictor of

AVF patency at 48h. Therefore, higher values of SBP seem to have a protective role on AVF outcome, probably due to a greater increase in shear stress and endothelium stimulation in an early phase. No associations were found with DBP. In a study with 742 patients, mean values of SBP and DBP inferior to 120/70mmHg were associated with an increased risk of failure (36.4% failures vs 9.16%) [44]. Our results show that PP and MAP had a higher correlation with SBP, as expected, but the best fitted multivariate models were obtained with SBP rather than DBP, PP or MAP.

On the ROC analysis, at 48h, a SBP cut-off of 154mmHg predicted AVF success with a sensitivity of 72.7% and specificity of 66.9%. The large confidence intervals show lack of precision, probably due to sample size. These findings, regardless of raising interesting hypothesis, should be interpreted with caution. Retrospectives studies do not offer evidence enough to change our clinical practice nor the current recommendations or guidelines. We observed that 154 mmHg was the optimized cut-of as predictor of AVF success. This means that even patients with normal blood pressure parameters have increased risk of AVF early failure compared with “permissive” hypertension. However, the risk/benefit of this approach is not addressed in this study and it should not be understood as a recommendation with immediate clinical implications.

The BP values refer only to the immediate pre-operative period, and subsequent measurements, along the AVF evolution, were not performed. It should also be taken into consideration that this is an extremely liable parameter and many factors influencing it, such as antihypertensive agents, were not controlled for or assessed, and may be confounding factors [72, 109]. From a clinical point of view,

the immediate pre-operative/intra-operative blood pressure is the value of most interest since it is the one that might change the clinical/surgical decision.

Venous diameter is a consistent predictive factor of AVF quality [147, 148]. The minimal venous diameter value predictor of radiocephalic fistulas success is 2.5mm. Failure rates of 16% on radiocephalic fistulas with <2mm of venous diameter, and a success rate of 76% in case the diameter was superior, have been reported [149, 150]. A mean venous diameter of 2,6mm has been associated to the failure of proximal AVF (*p=0.001*) [145].

Without considering other patient's characteristics, the venous diameter values that improve AVF probability of success range from 2.5-4mm. Most studies refer to distal AVF and have different measurement methodologies [145, 147-150]. In the present study, as described in the literature, AVF success at six weeks and twelve weeks was significantly associated with venous diameter in univariate analysis. The singular aspect in this study is that vein capacitance was indirectly studied by measuring in a standard and systematic method vein diameter with tourniquet and without tourniquet. AVF patency and AVF success both had higher VDT and VDWT. VDT and VDWT correlated with VD ratio and VD difference that were computed as a measure of vein capacitance. The best fit correlation was a negative exponential correlation between VDWT and VD ratio. This means that higher native VDs are associated with less capacitance measured by VD ratio. This raises more questions than answers since a higher native VD is associated with technical success and a higher capacitance should be associated with a higher functional success [145, 147, 149, 150]. In multivariate models, the best fit model excludes VDWT to include VDT with high significance, higher ORs, higher Youden Index, higher sensitivity and specificity with smaller confidence

intervals for AVF success at six weeks and twelve weeks. This suggests that VDT was the best independent predictor of clinical and functional AVF success. ROC curve analysis established 3.9mm as the optimal cut-off for vein diameter with tourniquet. These results are similar to those described in literature. However, the relative importance of VDT and VDWT is not usually address in other studies [151].

Taken together, these findings suggest that, from a technical point of view, SBP is an important landmark to surgical decision being predictor of 48h patency. However, from a functional and clinical point of view, VDT was the most important factor for AVF success at six weeks and twelve weeks.

Comparing AVF success at six weeks and twelve weeks with paired analysis showed that blood flow, resistance index and peak systolic velocity were not statistically different. However, vein diameter was higher at 12 weeks' assessment. This suggests that there is room for improvement between six weeks and twelve weeks. This is of utmost importance from a clinical decision point of view, meaning that, in some circumstances, patent although non-matured AVF at six weeks might mature until twelve weeks. If so, one should wait before planning an alternative AVF? Which might be unfeasible in patients with poor vascular beds. Otherwise, an alternative AVF? Should be considered as soon as possible.

In our sample only four patients showed a positive follow-up with a matured AVF after six weeks and before twelve weeks. This is too small a sample for subgroup analysis, but raises an important issue: which factors might predict a mature AVF after six weeks to avoid additional surgery? Which factors might predict that a

non-mature AVF will never mature to avoid additional time wasting before planning an AVF?

Although this is a prospective study with special attention to bias and confounders, with a similar sample size to prospective studies in the literature, with a specific aim usually not addressed (to define optimized cut-offs for pre-operative CDUS-derived parameters), multivariate models and ROC fit statistics (Omnibus qui-square and Youden index), it showed that additional non-measured factors interfere significantly with AVF patency and success.

CONCLUSIONS

CONCLUSIONS

- Age, gender, CKD etiology, CKD stage, presence of central venous catheters and comorbidities were not independent predictors of brachiocephalic and brachiobasilic AVF early success.

- The rationale expected correlations between arterial parameters, venous parameters and hemodynamic parameters lend consistency to CDUS and hemodynamic parameters assessment methods.

- AVF output vein diameter increase between six weeks and twelve-week period.

- Immediate pre- operative systolic blood pressure was an independent predictor of AVF patency at 48h, with an optimized cut-off of 154mmHg.

- Vein diameter with tourniquet was an independent predictor of 6 weeks and 12 weeks AVF success with an optimized cut-off of 3.9mm.

- Best fit statistics of multivariate models and ROC curve analysis were low to moderate which means that additional non-measured factors are important predictors of early AVF success.

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ANNEXES AND APPENDICES

ANNEX 1

Variables Operationalization Table

VARIABLE	DEFINITION CRITERIA	CODE
DEMOGRAPHIC AND CLINICA CARACTERIZATION		
Age		Age in years
Gender		male=1; female=2
CKD aetiology	Nephrologist evaluation	Description
Creatinine Clearance	Cockcroft-Gault equation	CrCl in mg/ml
CKD stage	KDOQI stages; I - CrCl > 90 mg/ml II – CrCl [60-90[mg/ml III – CrCl [30- 60[mg/ml IV – CrCl [15-30[mg/ml V – CrCl < 15mg7ml	I to V
HT	SBP ≥140 mm Hg or DBP ≥90 mm Hg or if taking anti-HT medication, or if the subject was told on 2 occasions that had HTA	0 – Absent; 1 – Present
Time since diagnosis of HT		Time in years
Controlled HT	Diagnosis of HT with SBP<140mmHg and SBP<90mmHg	0 – Not controlled; 1 – Controlled
COPD	GOLD 2017 - persistent signs and symptoms of respiratory and airflow limitation, namely chronic productive cough for 3 months in each of 2 successive years	0 – Absent; 1 – Present
HF	Diagnosed by the assistant nephrology or cardiology. NYHA classification.	I to IV

VARIABLE	DEFINITION CRITERIA	CODE
DEMOGRAPHIC AND CLINICA CARACTERIZATION (continued)		
DM II	ADA criteria: HbA1C≥6.5%,a fasting plasma glucose level of 126 mg/dl or higher; a 2-hour plasma glucose level of 200 mg/dl or higher during a 75-g oral glucose tolerance test or a random plasma glucose of 200 mg/dl or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis	0 – Absent; 1 – Present
Time since diagnosis of DM II		Time in years
Insulin therapy		0 – Oral Anti-DMII; 1 – insulin therapy
PAD	Fontaine classification I – asymptomatic II – intermittent claudication III – ischemic rest pain IV – ulceration or gangrene	I to IV
Anti-platelet therapy		0 – Absent; 1 – Present
Anti-coagulant therapy		0 – Absent; 1 – Present
BMI	Weight (kg) /height^2 (m)	BMI in kg/m2
Smoking status		0 – non-smoker; 1 – smoker; 2 – previous smoker
Catheters/Pace-Maker	Presence of Long Term Catheters or Pace-Maker	0 – Absence; 1 – contra-lateral; 2 – ipsilateral; 3 – Both

VARIABLE	DEFINITION CRITERIA	CODE
SURGICAL PROCEDURE VARIABLES		
Vascular Access		1 – brachiocephalic; 2 - brachiobasilic
Anastomosis		1 - Latero-terminal; 2 – Latero-lateral;
Surgical Complications	Unexpected events on the immediate post-operative period.	0 – Absent; 1 – Present (description)
PRE-OPERATIVE CDUS AND HEMODYNAMIC PARAMETERS		
VDT		mm
VDWT		mm
BAD		In mm
BAF		In l/min
Artery-vein distance		mm
VDT/VDWT ratio	VDT / VDWT	Ratio – no units
VDT/VDWT difference	VDT – VDWT	mm
SBP		mmHg
DBP		mmHg
PP	SBP-DBP	mmHg
MAP	(SBP+2*DBP)/3	mmHg
FOLLOW-UP CDUS (6 weeks and 12 weeks)		
AVF Flow	Measured at brachial artery	In l/min
Vein Diameter		In mm
Resistance Index	Measured at brachial artery	Ratio, no units
Pico-Systolic Velocity	Measured at brachial artery	In cm/second

VARIABLE	DEFINITION CRITERIA	CODE
OUTCOMES		
AVF 48h Patency	Continuous bruit and palpable thrill	0 – Not Patent; 1 – Patent
AVF 6W Patency	CDUS patency	0 – Not Patent; 1 – Patent
AVF 12W Patency	CDUS patency	0 – Not Patent; 1 – Patent
AVF 6W Success	CDUS evaluation: vein diameter ≥ 6mm and BAF≥600ml/s	0 – No Success; 1 – AVF Success
AVF 12W Success	CDUS evaluation: vein diameter ≥ 6mm and BAF≥600ml/s	0 – No Success; 1 – AVF Success

CKD – Chronic Kidney Disease; CrCl – Creatinine clearance; CKD – Chronic Kidney Disease; HT – Hypertension; SBP – Systolic Blood Pressure; DBP – Diastolic Blood Pressure; COPD – Chronic Obstructive Pulmonary Disease; GOLD – Global Initiative for Obstructive Lung Disease, HF - Heart Failure; DMII – Type II Diabetes Mellitus; ADA – American Diabetes Association; HbA1C – Glycosilated Hemoglobin (A1C); PAD – Peripheral Arterial Disease; BMI-Body Mass Index; VDT – Vein Diameter with Tourniquet; VDWT – Vein Diameter Without Tourniquet; BAD – Brachial Artery Diameter; BAF – Brachial Artery Flow; PP – Pulse Pressure; MAP – Mean Arterial Pressure; AVF – Arterio-Venous Fistula; 6W – six weeks; 12W – twelve weeks.

APPENDIX A

Pre-operative CDUS-derived parameters data registry protocol

Processo: **Exmo(a) Senhor(a):**

Data do Relatório:

Data do Exame:

Nº Episódio:

Serviço:

Tipo de Exame:

Informação Clínica:

Eco-Doppler arterial e venoso do membro superior esquerdo

Informação clínica: Mapeamento para construção de acesso vascular hemodiálise.

Relatório:

Arterial

As artérias subclávia, axilar, umeral, radial e cubital estão permeáveis e têm traçados trifásicos normais.

Artéria umeral tem um diâmetro de mm e um débito calculado de L/min.

A artéria radial tem um diâmetro de mm e um débito calculado de L/min.

A artéria cubital tem um diâmetro de mm e um débito calculado L/min

Venoso profundo

Veias umerais, axilar e subclávia permeáveis.

Venoso superficial

Veias cefálica e basílica permeáveis.

A veia cefálica mede, com garrote, no braço, mm. Dista mm da superfície cutânea e mm da artéria umeral. Sem garrote mede mm.

No antebraço a veia cefálica mede com garrote mm, dista mm da superfície cutânea e mm da artéria radial. Sem garrote mede mm.

A veia basílica mede com garrote mm, dista mm da superfície cutânea e mm da artéria umeral. Sem garrote mede mm. Drena para sistema venoso profundo no terço superior do braço.

APPENDIX B

Follow-up CDUS-derived parameters data registry protocol

Serviço
Imagiologia

PROF. DOUTOR FERNANDO FONSECA EPE
HOSPITAL

Processo: **Exmo(a) Senhor(a):**

Data do Relatório:

Data do Exame:

Nº Episódio:

Serviço:

Tipo de Exame:

Informação Clínica:

Eco-Doppler do acesso vascular hemodiálise do membro superior esquerdo

Os traçados obtidos nas artérias subclávia e umeral são monofásicos, com elevadas velocidades pico sistólicas e fluxo diastólico continuo, adequados a uma fístula arteriovenosa funcionante a jusante.

A artéria umeral tem mm de diâmetro e um débito calculado de l/min.

Identificou-se fístula arteriovenosa úmero basílica, com , permeável, na prega do cotovelo.

A veia basílica arterializada tem um diâmetro médio de mm.

As artérias radial e cubital estão permeáveis, com traçados bifásicos, com normal sentido do fluxo.

Médico:

Transcrito por

Validado por Médico - Imagiologia

APPENDIX C

Informed Consent Form

PROF. DOUTOR FERNANDO FONSECA EPE
HOSPITAL

CONSENTIMENTO INFORMADO PARA PARTICIPAÇÃO NO ESTUDO

"Factores Preditivos para sucesso nas fistulas arterio-venosas - utilidade da ecografia e Doppler"

Exmo(a). Sr(a).,

Neste momento os Serviços de Nefrologia, Radiologia e Cirurgia B do Hospital Prof. Dr. Fernando Fonseca, e Serviço de Cirurgia Vascular do Hospital Garcia de Orta, estão a realizar um estudo, no âmbito de um projeto de Mestrado em Epidemiologia, em doentes com insuficiência renal crónica submetidos a cirurgia para construção de acesso vascular definitivo para hemodiálise (fístula arterio-venosa). Este estudo tem por objetivo avaliar como alguns factores da ecografia e Doppler realizados antes da cirurgia podem influenciar o sucesso da fístula.

Após a informação sobre o processo lhe ter sido prestada oralmente, apresenta-se em seguida um resumo escrito das características deste estudo. Por favor, leia com atenção esta informação. Se, após ler esta informação, tiver quaisquer dúvidas, por favor coloque-as ao seu médico para que possam ser esclarecidas.

1) Descrição do processo e duração total da participação.

A sua participação no estudo consistirá apenas na realização de uma ecografia para avaliação da fistula às 6 semanas e 12 semanas após a cirurgia.

2) Benefícios de participar neste estudo

O(a) senhor(a) poderá não ter qualquer benefício ao escolher participar neste estudo, já que o que se está a estudar é se alguns factores da ecografia antes da cirurgia influenciam o sucesso da mesma.

No entanto, ao escolher participar neste estudo, estará a ajudar-nos a identificar factores que podem ajudar a decidir o melhor tipo de fístula a criar para cada doente, o que nos permitirá, futuramente, tratar de forma mais eficaz e melhor outras pessoas com insuficiência renal com necessidade de hemodiálise.

3) Participação voluntária

A sua participação neste estudo é totalmente voluntária. A escolha de participar ou não neste estudo é totalmente sua. O facto de escolher ou não participar neste estudo não vai alterar em nada a qualidade dos serviços e tratamentos que recebe neste Hospital. Caso escolha participar poderá desistir a qualquer momento, bastando para isso informar o seu médico.

4) Compensações

A sua participação neste estudo não terá quaisquer custos para si. As ecografias realizadas ser-lhe-ão oferecidas pela instituição. Não lhe será dada nenhuma compensação, monetária ou outra, pela sua participação neste estudo.

5) Confidencialidade

Todos os dados recolhidos durante este estudo são mantidos estritamente confidenciais, em suporte informático protegido. Se decidir participar neste estudo, ser-lhe-á atribuído um número de identificação único. Apenas o seu médico saberá que esse número único corresponde a si.

Após a conclusão do estudo, os dados recolhidos serão mantidos em suporte informático protegido durante dois anos.

6) Resultados do Estudo

Qua

ndo o estudo estiver concluído, os resultados e conclusões deste ser-lhe-ão comunicados.

7) Direito a recusar ou desistir

Como já lhe foi dito, a sua participação neste estudo é uma escolha exclusivamente sua. O facto de escolher ou não participar neste estudo não vai alterar em nada a qualidade dos serviços e tratamentos que recebe neste Hospital. Caso escolha participar poderá desistir a qualquer momento, bastando para isso informar o seu médico.

8) Contactos

Caso lhe surjam quaisquer questões futuras, seja durante a sua participação neste estudo ou depois de este ter terminado, por favor contacte o seu médico.

Dr. António Gomes

Serviço de Cirurgia B, Hospital Prof. Dr. Fernando Fonseca E.P.E.

Contactos: 214348312; antonio.p.gomes@hf.min-saude.pt

Estudo "Factores Preditivos para sucesso nas fistulas úmero-cefálicas – utilidade da ecografia e Doppler"

Por favor leia este formulário cuidadosamente

Por favor exponha as suas dúvidas ou informações adicionais que necessite

Médico: Nome e Apelido: _____

Participante: Nome e Apelido: _____

Declaração do participante

Recebi informação do meu médico, oralmente e por escrito, sobre os objectivos, procedimentos e possíveis vantagens e desvantagens da minha participação neste estudo.

Li e compreendi o consentimento informado. As minhas questões em relação ao estudo foram todas esclarecidas.

Recebi uma cópia do meu consentimento informado, assinado por mim.

Tive tempo suficiente para tomar a minha decisão.

Confirmo, com a minha assinatura, que aceito participar neste estudo.

Assinatura do Participante: _____

Data: _____

Estudo "Factores Preditivos para sucesso nas fistulas úmero-cefálicas – utilidade da ecografia e Doppler"

Declaração do médico

Transmiti a informação contida neste consentimento informado ao potencial participante e certifiquei-me que o participante compreende que:

a) será realizada uma ecografia para avaliação da fístula arteriovenosa às 6 semanas e 12 semanas após a cirurgia;

b) Confirmo que foi dada ao participante oportunidade de colocar questões sobre o estudo, e que respondi correctamente a todas as questões que o participante colocou;

c) Confirmo que o participante não foi de forma alguma coagido a participar neste estudo, e que o consentimento informado foi assinado pelo participante livre e voluntariamente.

O participante recebeu uma cópia do consentimento informado por si assinado.

Participante: Nome e Apelido: _____

Médico: Nome e Apelido: _____

Assinatura do Médico: _____

Data: _____

APPENDIX D

Hospital Prof. Dr. Fernando Fonseca Institutional Review Board approval

PROF. DOUTOR FERNANDO FONSECA EPE
HOSPITAL

PARECER DA COMISSÂO DE ÉTICA

TIPO DE ESTUDO: OBSERVACIONAL, PROSPETIVO, LONGITUDINAL, MULTICÊNTRICO.

TÍTULO DO ESTUDO:

Predictive Factors for Primary Patency in BrachioCephalic Fistula – Role of Colour Doppler Ultrasoud

Após reunião de 30 de Março de 2016, estando o estudo de acordo com as normas de submissão impostas por esta CE, deliberou-se emitir **parecer favorável** sobre a realização do mesmo.

Ouvido o Relator, o processo foi votado pelos Membros da Comissão de Ética para a Saúde do Hospital Prof. Dr. Fernando Fonseca, EPE presentes em reunião de 30 de Março de 2016:

Presidente	Dr. Silva Pereira
Vogais	Dr.ª Teresa Brandão
	Dr.ª Fernanda Louro
	Dr. Pedro Laranjeira
	Enf.ª Helena Cardoso
	Pe José Barros

Mais se declara que a Comissão de Ética para a Saúde do Hospital Prof. Dr. Fernando Fonseca, EPE, cumpre com as Normas da Boa Prática Clínica.

Pelo exposto, emitiu-se a 15 de Abril de 2016, **Parecer Favorável**.

O Presidente da Comissão de Ética

FERNANDO FONSECA HOSPITAL

Dr. José Silva Pereira
COMISSÃO DE ÉTICA

APPENDIX E

Lisbon Medical School Institutional Review Board approval

CENTRO ACADÉMICO
DE MEDICINA DE LISBOA

Presidente
Prof. Doutor José Pereira Miguel

Vice-Presidente
Profª. Doutora Maria Luísa Figueira

Membros
Prof. Doutor Alexandre Mendonça
Dra. Ana Luísa Figueiras
Prof. Dr. Carlos França
Padre Fernando Sampaio
Mestre Enfª. Graça Roldão
Prof. Doutor João Forjaz Lacerda
Prof. Doutor João Lavinha
Prof. Doutor José Luís Ducla Soares
Prof. Doutor José Luís Garcia
Profª. Doutora Mafalda Videira
Prof. Doutor. Mário Miguel Rosa

Exmo. Senhor
Dr. António Pedro da Silva Pinto Gomes
Rua de Belmonte, Nº 7 – 3º Dtº
2780-313 Santo Amaro - OEIRAS

Lisboa, 25 de Novembro de 2016

Nossa Refª. Nº 218/16

Assunto: Projecto de Investigação **"Predictive factors for primary Patency in BrachioCephalic Fistula – Role of color Doppler Ultrasound"**

Relator – *Prof. Doutor José Luis B. Ducla Soares*

Pela presente informamos que o projecto citado em epígrafe, a realizar no âmbito do projecto para Tese de Mestrado em Epidemiologia da Faculdade de Medicina da Universidade de Lisboa, obteve, na reunião realizada em 14 de Novembro de 2016, parecer favorável da Comissão de Ética.

Com os melhores cumprimentos,

O Presidente da Comissão de Ética do CAML

Prof. Doutor José Pereira Miguel

COMISSÃO DE
ÉTICA DO CENTRO ACADÉMICO DE MEDICINA DE LISBOA (CHLN/FMUL/IMM)
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